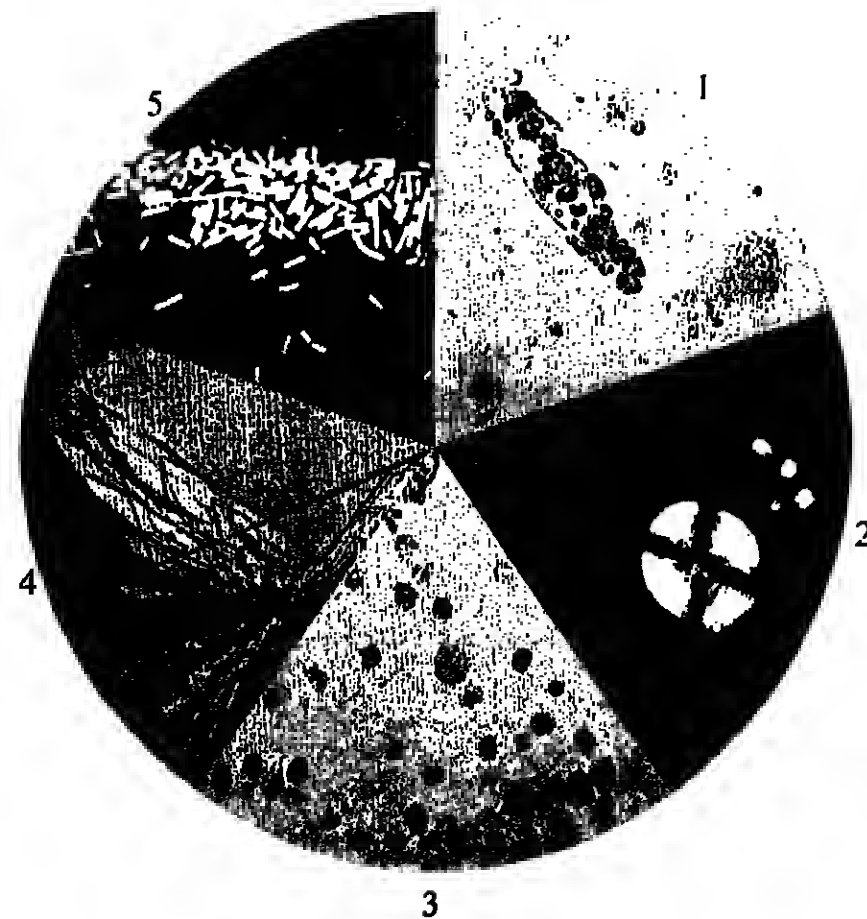


Clues to Clinical Diagnosis

Given the following findings...

1. White blood cell cast
2. Cholesterol crystals
3. White blood cells and red blood cells
4. Calcium phosphate
5. *E. coli*



...which would be the most likely clinical diagnosis? (Check one.)

- ☐ a. Acute glomerulonephritis
- ☐ b. Myeloma nephropathy
- ☐ c. Amyloidosis of kidney
- ☐ d. Chronic (active) pyelonephritis
- ☐ e. Acute tubular necrosis

See correct answer below.

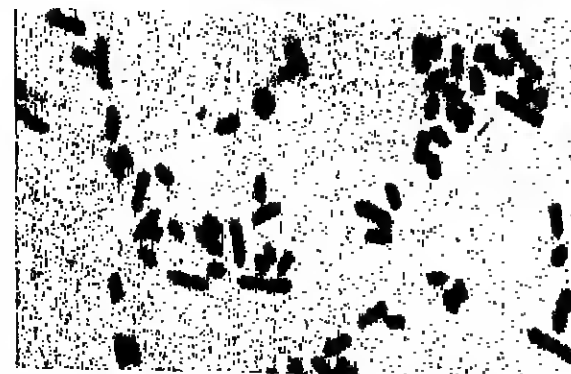
Clues to Urinary Tract Infection

When you see *E. coli* in significant amounts (10^5 /ml in 2 successive urine samples) and clinical signs and symptoms confirm your tentative diagnosis of urinary tract infection, initiation of antibacterial therapy is usually indicated.

For control of susceptible primary bacterial invaders. In nonobstructed pyelonephritis or cystitis, Gantanol® (sulfamethoxazole) is a logical choice, because Gantanol controls susceptible strains of such common urinary pathogens as *E. coli*, *Proteus mirabilis*, *Klebsiella-Aerobacter* and *Staph. aureus*.

For prompt antibacterial levels in blood and urine. Effective antibacterial levels of Gantanol in both blood and urine are usually established in from 2 to 3 hours after the initial 2-Gm adult dose.

Around-the-clock coverage for 14 days. Mounting evidence in current medical literature suggests a minimum of 14 days' continuous therapy for urinary tract infections.* Following the initial 2-Gm adult dose of Gantanol, each subsequent 1-Gm dose offers up to 12 hours of antibacterial therapy. Thus, Gantanol (either tablets or suspension), taken



morning and evening, provides coverage around the clock. This is especially important during the hours of sleep, when urinary retention favors bacterial proliferation. A t.i.d. dosage schedule is recommended for more severe infections.

For efficacy in acute, nonobstructed chronic and recurrent cystitis and pyelonephritis, when due to susceptible organisms. Gantanol tablets or pleasant-tasting suspension can provide your patients with

the dependable coverage they need. However, the usual precautions in sulfonamide therapy should be observed, including maintenance of adequate fluid intake, frequent c.b.c.'s and urinalyses with microscopic examination. The most common side effects include nausea, vomiting and diarrhea.

*Data on file, Hoffmann-La Roche Inc., Nutley, N.J.

Answer to quiz: d. Chronic (active) pyelonephritis.

In nonobstructed cystitis and pyelonephritis due to susceptible organisms

Gantanol (sulfamethoxazole) Basic Therapy

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with

microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: Blood dyscrasias (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); allergic reactions (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthritis and allergic myocarditis); gastrointestinal reactions (nausea, emesis, pancreatitis and stomatitis); CNS reactions (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, dizziness, vertigo and insomnia); miscellaneous reactions (drug fever, chills, toxic ophthalmia with oliguria and anuria, pericarditis, otitis media and L.E. phenomenon). Due to certain chemical similarities with some prodrugs, di-

retics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of galactosemia, diabetes and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). **Usual adult dosage:** 2 Gm (4 tabs or teasp.) initially, then 1 Gm b.i.d. or t.i.d. depending on severity of infection. **Usual child's dosage:** 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs b.i.d. Maximum dose should not exceed 75 mg/kg/24 hrs. **Supplied:** Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE Roche Laboratories Division of Hoffmann-La Roche Inc. Nutley, N.J. 07110

Medical Tribune

© 1975, Medical Tribune, Inc.

Vol. 16, No. 40

world news of medicine and its practice—fast, accurate, complete

and Medical News

Wednesday, November 12, 1975

At the PNHA National Assembly:



Dr. Jean Szilva, left, representative from Akron General Hospital, Ohio, discusses ulcerization at PNHA with Dr. Gaylard Nordline of the Northwestern University house staff, right.

'Sudden Onset' Tells Strep from Hyaline Disease

Medical Tribune Report

CHICAGO—The "sudden onset" of what seems to be hyaline membrane disease in a neonate may in fact signal the presence of group B streptococcal sepsis, an Illinois team warned here.

Calling for immediate initiation of antibiotic therapy in such patients, even prior to results of a culture, the team stressed that the usual clinical signs and symptoms suggestive of infection may often be "remarkably absent" in group B streptococcal sepsis.

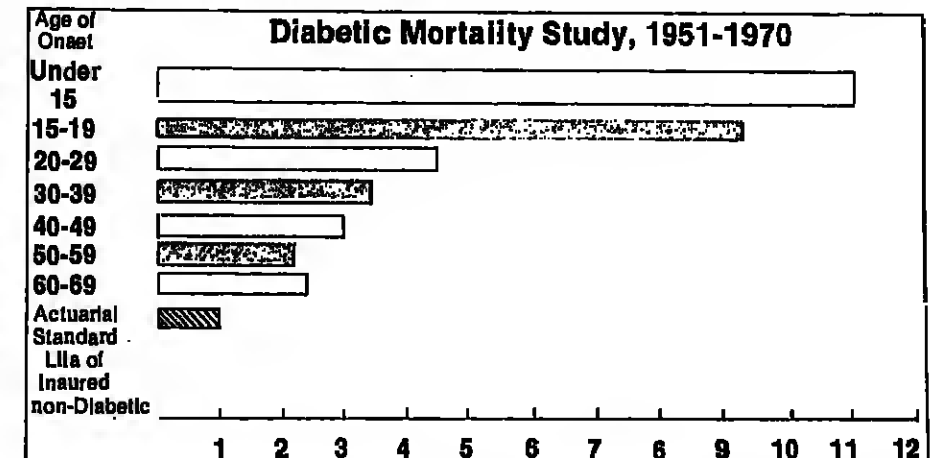
Presenting Symptoms

In the series of 11 infants described by Dr. S. I. Berman, Chief of Microbiology at St. Francis Hospital Center, Peoria, temperature instability, diarrhea, hepatosplenomegaly, and petechiae were not observed in any case. The most common presenting symptom was respiratory distress. Dr. Berman told the American Society of Clinical Path-

Continued on page 21

New Insurance Study Reveals

Sugar Control 'Important' to Survival of Diabetic Patients



Mortality Ratios Among Diabetics Compared With Actuarial Standard Lives By Age of Onset

Decreased life expectancy of diabetics is especially marked at earlier onset of disease, as shown in table above comparing mortality ratios of diabetics with those of standard insured non-diabetics. Data are based on prospective 20-year study of 10,538 diabetics. The diabetic with onset before age 15 has mortality ratio more than 11-fold greater than non-diabetic. Mortality in onset over age 60 is only two-fold greater.

By NATHAN HORWITZ

Medical Tribune Staff

Anti-Asthma Steroid Aerosol, Available Abroad, Withheld

Medical Tribune Report

NEW YORK—Canada's recent approval of beclomethasone, an anti-asthmatic steroid aerosol, leaves the United States the only major English-speaking nation in which the drug from the profession.

The British-developed compound, which avoids the systemic side effects of oral prednisone, has virtually replaced oral steroid therapy in the treatment of appropriate asthma patients in Great Britain, according to Dr. Timothy J. H. Clark, consultant physician to Guy's Hospital and Brompton Hospital, London.

Available in the United Kingdom since 1972, following three years of clinical trials, beclomethasone dipropionate is "probably being used now in almost the entire British population of asthmatics for whom it is indicated," Dr. Clark told MEDICAL TRIBUNE here. The drug has been approved for prescription use in all of the Scandinavian nations, West Germany and other European countries, and in Australia and New Zealand.

Dr. Clark, an internationally recognized authority in respiratory disease and a principal investigator in a continuing multi-center, double-blind British study of the drug, said the primary value of beclomethasone is that

it is a "systemic steroid-sparing agent." It is indicated for use in patients with uncomplicated asthma who respond to steroids.

The British multi-center studies, as well as recent American investigative trials, have shown that beclomethasone and a related compound, betamethasone valerate, controlled asthma symptoms while enabling patients to decrease or totally eliminate oral steroid doses, Dr. Clark said. The inhalants do

Continued on page 13

NEW YORK—In what is believed to be the largest mortality study of its kind, a major life insurance company has reported that a prospective, 20-year follow-up of more than 10,000 diabetics showed that blood sugar control is an "important factor" in the survival of the diabetic patient.

The finding, one of the highlights in the long-term nationwide investigation, disclosed that deaths among poorly controlled patients ran about two-and-a-half times higher than among those who were well controlled. Diabetes experts are in the midst of a controversy over the significance of control in the

Continued on page 2



CALIFORNIA CRISIS - 45% of state's MDs say they will quit or modify practice or leave the state if planned 48% increase in malpractice premiums takes effect Jan. 1 in southern Calif., according to Dr. Joseph Boyle, Pres. of the Calif. Medical Association. 10% of the state's doctors have already quit medicine or left Calif. and another 10% will be gone by Jan. Dr. Boyle said that

if doctors walk out, the state's 550 hospitals are doomed to bankruptcy. According to many state physicians, other breakdowns in the system -- refusal by doctors and hospitals to provide high-risk services, including delivering babies -- are imminent or already underway. While some physicians maintain that medical patients are a chief source of malpractice suits, Dr. Geoffrey Gordon, of the San Diego Council of Community Clinics, says his 17 free clinics have not had a litigated suit in 7 years.

PNHA president Dr. Robert Harmon speaks in favor of continued PNHA endorsement of candidates for the AMA Interns and Residents Business Section.

Housestaff Assn. Votes To Become National Union

Medical Tribune Report

WASHINGTON—When the National Assembly of the Physicians National Housestaff Association passed Resolution 15 by a unanimous voice vote, last month, there was silence, and then the

Continued on page 10

Control of Blood Sugar Extends Diabetics' Lives

Continued from page 1

development and course of diabetic complications and on survival.

Even when juvenile diabetics under age 30 were excluded from the data, mortality among poorly controlled patients totalled nearly twice that of the well-controlled group, according to the findings by the Equitable Life Assurance Society of the United States.

The report by Dr. George Goodkin, Equitable's associate medical director, was based on studies of 10,538 diabetics who applied for life insurance at Equitable between 1951 and 1970. It is the first prospective mortality study by the life insurance industry, according to Dr. Goodkin, in which both accepted and rejected applicants were followed to determine the mortality ratios for both groups.

Substandard Risk

The findings, "contrary to the opinion of some clinicians," confirmed that the diabetic, even if well-controlled, is a "heavily substandard risk, with a mortality ratio far in excess of normal," Dr. Goodkin said in his report, published in the November issue of the *Journal of Occupational Medicine*.

Overall, there were 1,478 actual deaths compared to 440.26 expected deaths for standard insured lives, a greater than three-fold difference. Rejected applicants had a four-fold mortality compared to standard expectations; and accepted diabetics (those who met underwriting criteria for insurability) had a death rate more than one-and-a-half times that of normal, Dr. Goodkin declared.

Among the other highlights revealed by the study were these:

- The finding of albuminuria in a diabetic is "an extremely unfavorable" prognostic sign.
- The mortality risk of hypertension in the diabetic is gravely multiplied when compared to the non-diabetic, especially at ages under 40.

In discussing the role of control in diabetes, Dr. Goodkin observed that the current controversy has resulted in different philosophies of management, ranging from that of strict control to free diet.

Juvenile vs. Adult Onset

"Some claim that strict control retards the long-range development of the complications of diabetes and therefore decreases mortality," Dr. Goodkin said. "Others contend that diabetic complications, especially the vascular changes, occur in the prediabetic stage of the natural history of the disease before there is any discernible abnormality... [and] they contend, therefore, that control of the metabolic abnormality cannot be a major factor in the development of complications."

Since juvenile diabetics have trouble maintaining good control of the increased severity of their disease, Dr. Goodkin declared, a question that had to be resolved was whether the increase in deaths in the poorly controlled cases was due to poor control or to the greater representation of severe juvenile cases. But when all juvenile di-

betics diagnosed under age 30 were omitted from the series, the mortality rate of poorly controlled patients was still almost double that of those who were well controlled.

"This small difference in mortality percentages between the juvenile diabetics and the maturity onset diabetics suggests that the difference in age distribution does not really account in any large measure for the highly excessive mortality in the poor control group, and that the two-and-a-half times increase in mortality of the poorly controlled group over that exhibited by the good control cases can be attributed mainly to the effect of control alone."

Commenting on some of the major findings, Dr. Goodkin noted that albuminuria and the early onset of diabetes were found to be associated with very high mortality ratios.

"Albuminuria showed a mortality ratio of 1031 per cent [more than 10 times that of standard insured applicants] and is a potent risk factor in diabetes, since it indicates the presence of renal complications and reflects the high mortality associated with Kimmelstiel-Wilson disease," he reported.

Hypertension, too, proved more ominous in the diabetic than in the non-diabetic patient, the report showed. In the groups with a diastolic of less than 90 mm, the mortality ratios increased with increasing systolic blood pressures: 267 per cent in those with a systolic of less than 140 mm., 334 per cent in those with a systolic of 140-159 mm. and 506 per cent in those with a systolic reading of 160 mm. or more. The same trend held true in the groups with a diastolic of 90 to 99 mm., the mortality percentages being 375, 418, and 459 per cent respectively.

Dr. Goodkin stressed, however, that there was a trend of decreasing mortality with increasing age at time of ap-

Elucidating Different Lymphocytes



T-cell or B-cell? Electron microscopists have reported they can differentiate between thymus-dependent and bone-marrow lymphocytes (T- and B-cells, respectively), the former by their smooth surfaces, the latter by the surface villi. But more recent studies suggest that the surface structures shown by the electron scanning microscope may differ widely, depending on the method of cell preparation. The photo above, for example, shows a T-cell rosette from a leukemia patient, but the T-cell, center, has the villous surface usually ascribed to B-cells. (photo by Drs. D. Belpomme and D. Duntelev, Villejuif, France.)

plication for insurance policy, suggesting "that this is an age-related effect."

Effect of Hypertension

He acknowledged that the data were suggestive but not sufficient to resolve the question whether hypertension in diabetics has a greater impact on mortality than in non-diabetics. He noted that the well-controlled, 35-year-old diabetic without complications has a mortality ratio of 247 per cent compared to the 100 per cent expected for the non-diabetic of the same age.

"The mortality ratio of the 35-year-old non-diabetic with a blood pressure of 150/95 is 195 per cent. If these were simply additive effects," Dr. Goodkin

observed, "the diastolic of the same age with a blood pressure of 105/95 would have a mortality ratio of 342 per cent. Our data, however, show it to be 1352 per cent—a difference of over 1000 per cent between the actual and expected mortality!"

"The difference is much smaller, however, for the well-controlled diabetic, age 50, with a blood pressure of 150/95, whose predicted mortality ratio is 221 per cent, while the actual mortality ratio was 296 per cent. The same trend holds true at all levels of increased blood pressure. Thus, it appears, hypertension has a greater adverse effect on mortality among diabetics than among non-diabetics."

New Agent Held Effective In Herpetic Keratitis

Medical Tribune Report

DALLAS—Trials of vidarabine (adenine arabinoside) in the treatment of herpetic keratitis indicate that this new agent equals idoxuridine (IDU) in effectiveness and furthermore will benefit a high percentage of patients who either cannot tolerate or are resistant to the other drug.

Reporting here on results seen in 315 patients, Dr. Deborah Pavan-Langston of Harvard Medical School said the trials had included a double-blind study of 169 patients, designed to compare the effects of IDU with those of vidarabine, and an open study in which vidarabine was the only ointment used.

Although vidarabine has been obtainable only for experimental purposes, it has now been approved by the Food and Drug Administration and is expected to be available soon.

Findings from the double-blind trial showed "no significant difference" between the two antiviral agents in mean time for complete epithelial healing and the percentage of patients achieving corneal re-epithelialization, Dr. Pavan-

Langston told the American Academy of Ophthalmology and Otolaryngology.

The investigator also noted that the drugs had approximately the same effect in relieving symptoms of lacrimation, photophobia, and sensitivity. However, the proportion of patients whose distant visual acuity improved was significantly higher in the vidarabine group (66.2 per cent) than in the IDU group (43.5 per cent).

Lacrimation Dropped

All 146 patients in the open study had acute or recurrent active epithelial herpetic keratitis, and the severity of their disease was greater than in the double-blind group as measured by size of ulcers and duration of symptoms, according to Dr. Pavan-Langston. Nearly 80 per cent were known to be intolerant of, or resistant to, IDU.

With vidarabine treatment, the proportion of those showing lacrimation dropped sharply from 90 per cent to about 23 per cent at the end of therapy. Similar reduction in the incidence of other symptoms was observed. Visual acuity improved in slightly more than

half of the 90 patients evaluated.

Approximately 95 per cent of dendritic and dendritico-geographic ulcers cleared during four weeks of treatment but only 60 per cent of geographic ulcers did so.

Most significantly, in Dr. Pavan-Langston's view, re-epithelialization occurred within four weeks after the start of therapy in 91 of the 116 patients for whom previous IDU treatment had been either toxic or ineffective.

"In the past," she said, "IDU failures were often attributed to patient neglect of medication schedules, inadequate drug levels because of poor solubility, and rapid in situ metabolism. But now it appears that many failures result from simple resistance or intolerance to the only commercially available antiviral medication—IDU."

Although some patients had adverse experiences with vidarabine—as with IDU—the investigator pointed out that a number of these were disease related and not drug induced. No patients displayed significant toxic reactions to vidarabine "even after 192 days of continuous use," she emphasized.

Needles for Nerve Block Found 40% Wrongly Placed

By HILDA LASS
Medical Tribune World Service

FLORENCE, ITALY—There is a 40 per cent chance of error in needle placement when nerve block sites are selected by the classical method of geometrical formulas based on anatomical landmarks, according to Dr. Verne Brechner, Professor of Anesthesiology, and Dr. Theresa Ferrer-Brechner, Assistant Professor, U.C.L.A. School of Medicine.

Thirty patients who received either diagnostic or therapeutic nerve blocks at the U.C.L.A. Pain Management Clinic were studied. The placements were performed without the aid of fluoroscopy, adhering to the landmarks recommended in a standard textbook, the investigators told the First World Congress on Pain Research and Therapy.

X-rays Suggested

Following placement, fluoroscopy was carried out and permanent X-rays taken. The needle was repositioned if necessary and local anesthetic injected, sometimes with contrast medium. The overall score was 12 incorrect placements, or 40 per cent, they stated.

The most consistently inaccurate was the stellate ganglion block, correctly placed in five out of six patients. The highest incidence of error occurred with the lumbar somatic block (four out of five), where the most common error was placement of the needle in the wrong interspace.

Since somatic nerve blocks are used to predict the results of rhizotomy, an incorrectly located block could result in severing the nerve at the wrong level, and this could be one reason for the 25-45 per cent failure in posterior rhizotomy cited by some authors, the investigators believe. X-rays should

therefore be taken during the placement of somatic blocks, they concluded.

Noninvasive Therapy

► The development of new, noninvasive types of pain therapy and advancement in the understanding of pain mechanism will limit the clinical use of nerve blocks, said Dr. John J. Bonica, Professor of Anesthesiology and director of the Pain Clinic at the University of Washington School of Medicine.

Although nerve blocks will continue to play a prominent role in treating certain types of acute and chronic pain, the real future of the technique lies in its potentialities as a research tool, said Dr. Bonica, who during the congress was voted President-Elect of the International Association for the Study of Pain, formed a year ago.

"We can and should restudy the sensory supply to various structures of the body," he continued, "using nerve blocks and the improved regional techniques, new anesthetics, advanced radiography, and the sophisticated neurophysiologic recording techniques currently available."

Two factors have impeded the use of blocks to study pain mechanism, Dr. Bonica said. First, "Most investigators have not realized that techniques are available to interrupt discretely virtually every spinal, cranial, sympathetic or parasympathetic nerve pathway in the body." Second, "Regional anesthesia has hardly been taught in the past three decades so that many anesthesiologists lack the training to execute most of the blocks."

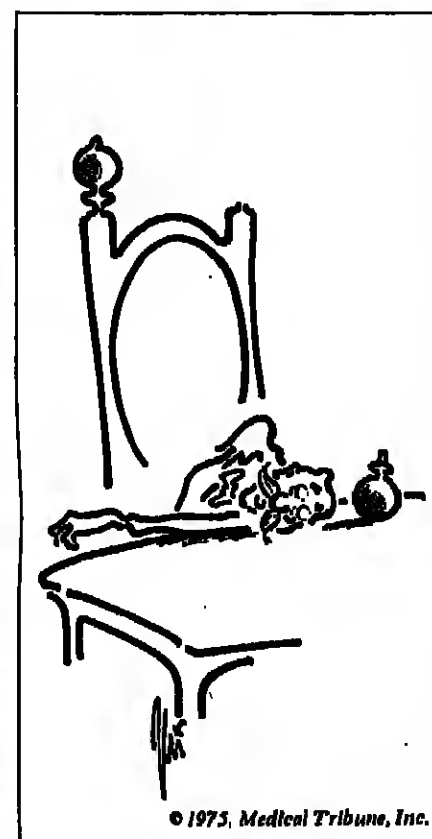
In pain therapy, Dr. Bonica said, blockade of the sympathetic pathways is likely to remain one of the best ways of treating causalgia and other reflex

sympathetic dystrophies, and, to a lesser extent, acute herpes zoster and post-herpetic syndrome. "Celiac plexus block will also continue to be useful in the diagnosis of obscure abdominal pain, in severe pain in acute and chronic pancreatitis and cancer," he said.

Block of specific spinal nerves in the paravertebral region will be useful in diagnosis and prognosis, he continued. Intercostal nerve block will have its place in controlling acute pain due to fractures, in postoperative pain of the thorax and abdomen, and in the management of postoperative, post-traumatic and postinfectious neuralgia, he added.

Subarachnoid Block

► Relief of cancer pain by subarachnoid block with alcohol or phenol
Continued on page 5



© 1975, Medical Tribune, Inc.

Spleen May Suppress Body's Defenses

By ANASTASIA TOUPXIS
Medical Tribune Staff

WASHINGTON—"The chronic nature of some infectious diseases may be due to suppression of the body's defenses by the spleen," Dr. David J. Wyler of the National Institute of Allergy and Infectious Diseases, Bethesda, Md., told a meeting here of the American Society for Microbiology.

"We've known for some time that the spleen plays a protective role in the acute stages of infection, and our own investigation confirms this, but this is the first time an inhibitory role has been demonstrated," he said.

Speaking for colleagues Dr. Louie H. Miller, also of NIAID's Laboratory of Parasitic Diseases, and Prof. Leon H. Schmidt of the Southern Research Institute, Birmingham, Alabama, Dr. Wyler said these conclusions were drawn from a study of the course of infection in rhesus monkeys inoculated with *Plasmodium lutz*, a monkey parasite similar to *P. malariae*.

In man, *P. malariae* causes quartan malaria, a type of malaria characterized by fever every 72 hours, Dr. Wyler explained. If untreated, the infection may

persist for as long as 50 years.

Seventeen monkeys had their spleens removed prior to intravenous inoculation with parasitized erythrocytes while another 19 were splenectomized after infection. A third group of 40 infected monkeys were left intact.

"We found that the spleen exerted a protective effect during the acute stages of infection," Dr. Wyler said. "While both groups of splenectomized monkeys consistently had ten-fold higher peak parasitemias than did intact animals, a high mortality at the peak of infection occurred only in the group with spleens removed prior to inoculation."

'Unexpected Finding'

The rate of parasite clearance after peak parasitemia was similar in all surviving animals, regardless of which group they were in, he added.

"But," Dr. Wyler continued, "the totally unexpected finding was that splenectomized monkeys achieved self-cure within a year while intact animals had persistent infection, lasting up to 16 years, in association with low cure rates in the first five years."

While these observations suggest that the spleen in quartan malaria has both protective and suppressive functions, its role in infectious disease in general is very confused, Dr. Wyler told MEDICAL TRIBUNE.

"Until recently, the thought was that the spleen functioned as an organ to trap bacteria and other organisms circulating in the blood. More recently, basic immunology studies suggest that certain types of antibodies are produced by the spleen. And when the spleen is removed, the body's immune system is compromised," he said.

Dr. Wyler is presently on leave from NIAID and in Boston at Massachusetts General Hospital, engaged in a retrospective analysis of patient charts. "One interesting thing is that it's becoming clear that when the spleen is removed before the age of two, and sometimes five, the child is more susceptible to infection. In adults, the effect of spleen removal is less clear."

The investigators speculate that the spleen's opposing roles in protection and suppression may relate to the immunologic balance between the functions of T- and B-cells in the spleen.

index

CLINICAL NEWS NOTE: "Hopefully, with the widespread use of beclomethasone in the rest of the Western world—as well as the English-speaking Pacific nations—the F.D.A. should come to a speedy conclusion as to its efficacy. It has been reviewed and approved by the regulatory agencies of the U.K., Australia and Canada, to name only some, and there should be enough evidence on which the F.D.A. can base a judgment. If not, the F.D.A. ought to advise the other regulatory agencies what to look for, because the F.D.A.'s hesitation suggests that the other agencies have been remiss in some important respects." (Dr. Timothy J. H. Clark, consultant physician, Guy's Hospital, London. See page 1.)

Medicine: 1, 2, 3, 10, 17, 24
Blood sugar control held "important" to diabetic survival 1
Housestaff Association votes to become a national union 1
Herpetic keratitis effectively treated with new agent, vidarabine 2
Hyperglycemia therapy with somatostatin seen as coming in the near future 17
"Unexplained" fever in cancer patients laid to hidden infection 24

Pediatrics: 1
Apparent hyaline membrane disease may actually be strep B infection 1

Surgery: 8
Early repair of "dashboard knee" may prevent subsequent degenerative arthritis 8

Obstetrics: 9
Prenatal diagnosis not used in 99 per cent of pregnant women at high risk 9

Psychiatry: 16
Emotional problems cause a high number of residents to drop out 16

feature index

Editorial Capsules 8
Editorials 11
Current Opinion 14
One Man...and Medicine 17
Ellot Janeway 20
Sports Report 23

Medical Tribune

CHRIS WOODBURY, Ph.D.
General Manager

HARRY HENDERSON, Editor-in-Chief
RICHARD GUNNER, M.D., Associate Editor
HAROLD FOSNOT, Editor
JOHN HEWITT, Executive News Editor
Associate News Editor
WILLIAM FAFFER, Art Supervisor
ANN CONNER, Picture Editor

ARTHUR M. SACKLER, M.D.
International Publisher

Advisory Board
JOHN ADRIANI, M.D., • ERNE J. DUBOS, Ph.D.
JULIUS H. MASSEMAN, M.D.
BERNARD LOWN, M.D.
ALBERT B. SARIN, M.D.
ALTON OCHNER, M.D.
ROBERT A. CHAM, M.D.
LEO G. ROHLER, M.D.

880 Third Avenue, New York, N.Y. 10022
Telephone: 421-4000
Circulation audited by Business Publications Audit of Circulation, Inc.

MEDICAL TRIBUNE is published each Wednesday except on April 30, July 9, July 30, Aug. 13, Oct. 29 and Dec. 31 by Medical Tribune, Inc., 880 Third Avenue, New York, N.Y. 10022. Controlled circulation postage paid at Vineland, N.J. 08360. Subscription \$25.00, Students \$7.50.

Nobel Explorer Lysosome Role in Rheumatic Disease

Medical Tribune World Service

HELSINKI—Reviewing the role of lysosomal inflammatory processes in rheumatic diseases at the 8th European Rheumatology Congress here, Nobel laureate Christian de Duve explained three mechanisms by which lysosomes are involved in pathogenicity and suggested possible therapeutic applications of these digestive vesicles found in all animal cells.

One such mechanism is lysosomal overloading, Dr. de Duve said. It occurs when lysosomes take up material they cannot digest, when there is an imbalance in substrate and enzyme activity, or when an enzyme is deficient genetically or has been poisoned. This mechanism might be responsible for "choking a cell to death" after injection of certain drugs.

Another mechanism, he said, is rupture of the lysosomal membrane, such as by injury. This probably happens in gout.

Enzyme Discharge

A third mechanism—of particular importance in rheumatic diseases—is the discharge of enzymes from the lysosomes to the extracellular spaces. These enzymes attack extracellular components if the cell inhabits a stagnant environment or if the environment is favorable to the activity of the enzymes.

"On the basis of what we suspect, rather than what we know, in the pathogenesis of rheumatic diseases," said Dr. de Duve, "we can theoretically think of intervening at different levels."

The most immediate therapeutic application would be inhibition of the activity of the enzymes that have been released extracellularly.

Another level of intervention, he said, might entail preventing extracellular release of enzymes. This release could be inhibited by changing the physical properties of the membranes, perhaps making them more rigid and less able to fuse, or by inhibiting the machinery that activates the fusion phenomenon.

"We know very little about this machinery," Dr. de Duve said, "but there is some evidence that cyclic AMP inhibits fusion and that cyclic GMP stimulates fusion. So possibly by changing the levels of the cyclic nucleotides in the cell with certain drugs you may be able to influence the fusion phenomenon."

It is known, for example, that prostaglandins influence the levels of cyclic nucleotides and that aspirin inhibits the synthesis of prostaglandins, said Dr. de Duve. "And so it is not impossible that prostaglandins may act on some lysosomal mechanisms by way of cyclic nucleotides, and that salicylates somehow prevent these mechanisms by acting on the prostaglandins. But this is hypothetical."

Dr. de Duve currently serves with Rockefeller University in New York. He shared the Nobel Prize in Physiology and Medicine in 1974 with Albert Claude and George Palade.

MEDICAL TRIBUNE

Wednesday, November 12, 1975

SLEEPING BETTER...

THE BEGINNING OF THE END OF CLINICAL DEPRESSION/ANXIETY

Even before it helps her clinical depression/anxiety, Sinequan (doxepin HCl) can help her sleep through the night.

The sedative effect of Sinequan usually helps clinically depressed/anxious patients with accompanying sleep disturbances fall asleep more easily, remain asleep, and awaken more rested.

Administering the major portion of the daily dose h.s. generally obviates the use of supplementary hypnotic agents.

The marked anxiolytic property of Sinequan is particularly helpful in relieving apprehension, tension and worry. Optimal antidepressant effect is usually seen two to three weeks after initiation of therapy.

SINEQUAN[®]

DOXEPIN HCl

10 mg., 25 mg., 50 mg. and new 150 mg. capsules

BRIEF SUMMARY Sinequan[®] (doxepin HCl) Capsules

Contraindications. Sinequan is contraindicated in individuals who have shown hypersensitivity to the drug.

Sinequan is contraindicated in patients with glaucoma or a tendency to urinary retention.

Warnings. *Usage in Pregnancy:* Sinequan has not been studied in the pregnant patient. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient, although animal reproductive studies have not resulted in any teratogenic effects.

Usage in Children: The use of Sinequan in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with Sinequan (doxepin HCl). The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of that possibility and cautioned against driving a car or operating dangerous machinery while taking this drug.

Patients should also be cautioned that their response to alcohol may be potentiated. Since alcohol is an inherent risk in any depressed patient and may remain so until

significant improvement has occurred, patients should be closely supervised during the early course of therapy.

Although Sinequan (doxepin HCl) has significant tranquilizing activity, the possibility of activation of psychotic symptoms should be kept in mind.

Other structurally related psychotherapeutic agents (e.g., iminodibenzyl and dibenzocycloheptenes) are capable of blocking the effects of guanethidine and similarly acting compounds in both the animal and man. Sinequan, however, does not show this effect in animals. At the usual clinical dosage, 75 to 150 mg. per day, Sinequan can be given concomitantly with guanethidine and related compounds without blocking the antihypertensive effect. At doses of 300 mg. per day or above, Sinequan does exert a significant blocking effect. In addition,

Sinequan (doxepin HCl) was similar to the other structurally related psychotherapeutic agents as regards its ability to potentiate norepinephrine response in the animal. However, in the human this effect was not seen. This is in agreement with the low incidence of the side effect of tachycardia seen clinically.

Adverse Reactions. Anticholinergic Effects: Dry mouth, blurred vision, and constipation have been reported. They are usually mild, and often subside with continued therapy or reduction of dose.

Central Nervous System Effects: Drowsiness has been observed. This usually occurs early in the course of treatment, and tends to disappear as therapy is continued.

Cardiovascular Effects: Tachycardia and hypotension have been reported infrequently. Other infrequently reported side effects

include extrapyramidal symptoms, gastrointestinal reactions, secretory effects such as increased sweating, weakness, dizziness, lethargy, weight gain, adams, paraesthesiae, flushing, chills, tinnitus, photophobia, decreased libido, rash, and pruritus.

Dosage. For most patients with illness of mild to moderate severity, a starting dose of 25 mg. i.t.d. is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg./day to 150 mg./day.

In more severely ill patients an initial dose of 50 mg. i.t.d. may be required with subsequent gradual increase to 300 mg./day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg./day.

In patients with very mild symptomatology

or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg./day.

Although optimal antidepressant response may not be evident for two to three weeks, anxiolytic activity is rapidly apparent.

Supply. Sinequan (doxepin HCl) is available as capsules containing doxepin HCl equivalent to 10 mg., 25 mg., 50 mg., and 100 mg. of doxepin in bottles of 100, 1000, and unit-dose packages of 100 (10 x 10's).

More detailed professional information available on request.

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017
© 1974, Pfizer Inc.

Needles Found 40% Wrongly Placed In Nerve Block

Continued from page 3

should be limited to patients in the terminal stage of the disease and applied only in those patients with advanced metastatic cancer with clearly monolateral and well-circumscribed pain. Prof. Vittorio Venturini, director of the Pain Therapy and Rehabilitation Department, National Tumor Institute, Milan, reported. Results are difficult to predict as they depend upon the direct or indirect involvement of various types of nerve fibers, and complications are frequent.

Of 227 patients in whom 319 neurolytic blocks were performed, complete remission of pain for at least six days was recorded in only 56 per cent. The average duration of pain relief was 15.4 days. There were temporary complications (bladder or rectal disturbances, muscle weakness, paresthesia) in 40 per cent of cases.

With good positioning and correct needle placement, this technique still holds a limited place in cancer pain therapy, Dr. Venturini concluded. However, when the patient is still in good general condition and has not reached the terminal stage, other methods should be chosen.

Co-author was Dr. G. Martino, also of the National Tumor Institute, Milan.

In Herpes Zoster

► Neurolytic blocks are still the most effective treatment of acute herpes zoster and the best prevention for postherpetic neuralgia, said Prof. Willy H. Dini of the department of anesthesiology, Bispebjerg Hospital, Copenhagen. He reported a follow-up study of 311 out of 378 patients treated in the past decade.

Of these, 279 acute cases were treated with 86 per cent success. Only 14 per cent of all patients treated with blocks later developed postherpetic syndrome. All patients below the age of 50 were cured and there was no significant difference in the incidence of failure between 50 and 79 years of age. There were too few patients over 80 to draw any conclusions.

No significant correlation was found between the location of the disease and the results of treatment, or between the location of the disease and age, Dr. Dini pointed out.

Acute cases were treated with stellate blocks for herpes zoster localized at the trigeminal nerve, or with lumbar sympathetic blocks if the disease was localized at the lumbosacral plexus. Carbocaine (1 per cent without vasoconstrictor) was used. For intercostal blocks, a combination of 20 per cent ammonium sulphate and 2 per cent carbocaine was employed.

The patients received five blocks a week up to a total of 18 blocks. Skin eruptions usually dried up within a week, and pain disappeared after an average of 12 blocks.

Postherpetic syndrome was treated with 8 per cent phenol in water or 97 per cent alcohol injected in the somatic nerves involved, as close as possible to the cranium or spinal canal.

Salerno, Normandy, Iwo Jima, Inchon.

And still one more battle...



Top, left to right: Medal of Honor (Army), Silver Star, Legion of Merit. Bottom, left to right: Bronze Star, Air Medal, Purple Heart. Permission to reproduce medals granted by U.S. Department of Defense.

References
1. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202: 1028-1034, 1967.
2. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213: 1143-1152, 1970.
3. Russell RP: Hypertension, in Harvey AM, Johns RJ, Dienes AH, et al (eds): *The Principles and Practice of Medicine*, ed 16. New York, Appleton-Century-Crofts, 1972, pp 331-334.
4. Gifford RW: Drugs for arterial hypertension, in Modest W (ed): *Drugs of Choice*, 1972-1973. St. Louis, The CV Mosby Co, 1972, pp 390-393.
5. Sattler AM, Jiskovitz HD, Lindauer MD: Systemic arterial hypertension, in Conn FL Jr, Horwitz O (eds): *Cardiac and Vascular Diseases*. Philadelphia, Lea & Febiger, 1971, vol II, pp 934-943.

Ser-Ap-Es®

reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

INDICATIONS
Hypertension. (See box warning.)

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy initiated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

CONTRAINDICATIONS
Reserpine: Known hypersensitivity; mental depression (especially with antidepressant therapy); active peptic ulcer; ulcerative colitis; electroconvulsive therapy.

Hydralazine: Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.

Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Reserpine: Use with extreme caution in patients with a history of mental depression. Discontinue at first sign of despondency, early morning insomnia, loss of appetite, impotence, or self-depression. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide. MAO inhibitors should be avoided or used with extreme caution.

Hydralazine: Chronic administration of doses over 400 mg daily may produce an arthritis-like syndrome affecting distal systemic lupus erythematosus. This may also occur at lower doses. Long-term treatment with steroids may be necessary and relapses have been detected many years later. CBCs, ECG preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine or if the patient develops any unexplained signs or symptoms.

Hydralazine: Use with caution in patients with severe renal disease. In patients with renal disease, hydralazine may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides: Should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.

Thiazides: May be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with thiazide or peripheral adrenergic blocking drugs.

Sensitivity reactions: are more likely to occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Reserpine: The safety of reserpine for use during pregnancy or lactation has not been established; therefore, the drug should be used in pregnant patients or women of childbearing potential only when, in the judgment of the physician, it is essential to the welfare of the patient.

of the patient. Increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in neonates, jaundice, and breast-fed infants. If reserpine-treated mothers since reserpine crosses the placental barrier and appears in maternal breast milk.

Hydralazine: The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.

Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Reserpine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Hydralazine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Hydrochlorothiazide: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Thiazides: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Reserpine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

Hydralazine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

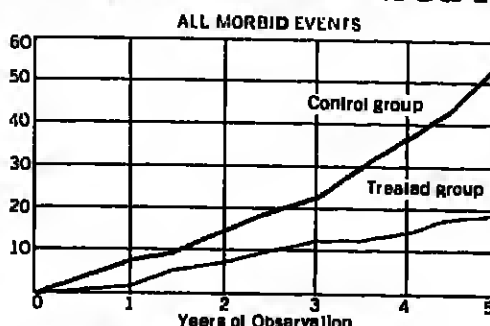
Hydrochlorothiazide: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).

The battle against hypertension...

The VA studies demonstrated the need for therapy.^{1,2}

In the VA study of 1967,¹ the patients were 145 male veterans with diastolic pressures averaging 115 through 129 mm Hg. In this group of patients with moderately severe elevations of pressure, antihypertensive therapy appeared to exert significant benefit.³

Further, in the study of 1970,² which examined effects of treatment in males with diastolic pressures averaging 90 through 114 mm Hg, it was found that patients in these lower hypertensive ranges clearly benefited from therapy. The estimated risk of developing a morbid event over a 5-year period was reduced from 50% to 18%. Degree of benefit was related to pre-treatment blood pressure levels.⁴



Estimated cumulative incidence of all morbid events over a five-year period as calculated by life-table method for patients with diastolic pressures averaging 90-114 mm Hg. (Adapted)

Control was achieved^{1,2} with...

hydrochlorothiazide

provides a mild antihypertensive effect through control of fluid volume; potentiates the activity of other antihypertensive agents.^{5,6}

(a) Symbolized reduction in circulating fluid volume

plus reserpine

lowers blood pressure through sympathetic inhibition;^{7,8,9} also produces a central sedative effect which may prove particularly useful in the management of the stress-reactive patient.

(b) Schema of reserpine-pyridine depletion of sympathetic nerve ending



plus hydralazine

the unique action of hydralazine lowers blood pressure through direct arteriolar vasodilation to reduce peripheral resistance.^{10,11}

(c) Diagram of relaxed arteriole

Only one antihypertensive agent contains all three components used in the two published VA cooperative studies.^{1,2}

In the VA studies, Ser-Ap-Es was not used. However, all the components of Ser-Ap-Es were used in varying combinations and dosages.^{1,2}

Ser-Ap-Es contains all the antihypertensive medication many patients will need.

And when the dosage of each component corresponds to the dosages preestablished by individualized titration, Ser-Ap-Es may prove more convenient and more economical.

The basic drugs used in the VA studies — hydrochlorothiazide, reserpine, and hy-

dralazine — are original products of CIBA research.

Note: Use Ser-Ap-Es cautiously in patients with advanced renal damage or cerebrovascular accident. Discontinue at first sign of mental depression.

Ser-Ap-Es®

reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

Periodic blood counts are advised during prolonged therapy. Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of renal or electrolyte imbalance (hypokalemia, hypochloremic alkalosis, and hyponatremia). Serum and urine electrolyte determinations are particularly necessary when the patient is vomiting, receiving therapy with diuretics, or receiving concomitant administration of steroids or ACTH. Indication such as digitalis may

also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting. Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe circulatory is present, or during concomitant administration of steroids or ACTH. Interference with adequate oral intake

of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the

hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy. Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or

unchanged. Latent diabetes may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Reserpine: Gastrointestinal — hypersecretion; nausea; vomiting; anorexia; diarrhea. Cardiovascular — angina-like symptoms, arrhythmias (particularly when used concurrently with digitalis or quinidine); bradycardia. Central Nervous System — drowsiness; depression; nervousness; paradoxical anxiety; nightmares; rare parkinsonian syndrome and other extrapyramidal tract symptoms. CNS sensitization (manifested by dull sensorium, deafness, glaucoma, uveitis, and optic atrophy).

Hydralazine: Common — headache, palpitations, anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. Less frequent — nasal congestion, flushing, lacrimation, conjunctivitis, peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremor; nervousness; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, erythema, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; cyanosis; pericardial effusion; lymphadenopathy; epistaxis; megaloblastic anemia; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

Hydrochlorothiazide: Gastrointestinal — anorexia; gastric irritation; nausea, vomiting; cramping; diarrhea, constipation, jaundice (intrahepatic cholestasis, pancreatitis). Central Nervous System — dizziness, vertigo, paresthesias, headache, xanthopsia. Dermatologic — hypersensitivity — purpura, photosensitivity, rash, urticaria, necrotizing angitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. Hematologic — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. Cardiovascular — orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. Other — hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSEAGE: As determined by individual titration (see box warning). Usual dosage is 1 or 2 tablets t.i.d. For maintenance, adjust dosage to lowest patient requirement. When necessary, more potent antihypertensives may be added gradually in dosages reduced by at least 50 percent.

HOW SUPPLIED
Tablets (dark salmon pink, dry-coated), each containing 0.1 mg reserpine, 25 mg hydralazine hydrochloride, and 15 mg hydrochlorothiazide; bottles of 30, 60, 100 and 1000.

Consult complete literature before prescribing.

CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07991.

C I B A

Medical Tribune World Service

© 1975, Medical Tribune, Inc.

Housestaff Assn. Votes To Become Union

Continued from page 1

hundred-odd delegates broke into applause, cheers, and whistles.

Dr. Robert Harmon, president of the three-year-old national house officers' organization, looked over at the group's presiding officer, vice president Dan Asimus, and sighed. "We've done it," he said. "We've done it!"

What the two officers—and the delegates from local house staff associations across the country—had done was to pass the final resolution necessary for the PNHA to become a national union.

The delegates showed their approval of unionization again the following day when they re-elected Drs. Harmon and Asimus to their posts. That vote too was unanimous; the two house staffers were unopposed in their bids.

Year-Long Effort

The passage of Resolution 15 marked the end of a year-long effort by PNHA officers, committee members, and staff. They had begun their work almost before the shouting died down at last year's National Assembly meeting, in Kansas City. There the house staff representatives set up two committees: one to study the PNHA constitution and make recommendations for changes, the other to explore taking a ride on the union train.

Within a matter of months, the two committees had become one, and the constitution and bylaws section spent its time researching the changes required by the National Labor Relations Act and writing them into a new document. As a result, the constitution and bylaws were almost totally rewritten, and three quarters of the National Assembly's business in Washington involved deliberating over and passing on the changes.

Delegates to the National Assembly came to Washington prepared for the business at hand. When they learned that their local associations would not have to become formal unions—which they were reluctant to do in some areas and legally barred from in others—to belong to the PNHA, they gave the move their full support.

"It isn't as if we all came here sold on unionism," pointed out Dr. Dan Fink of Cincinnati General Hospital. "There's a wide diversity of opinion here, and we voted for this with a certain degree of trepidation. Now we have to go back to our local house staffs, and how they react will depend on how we present it."

Strong National Group

Some delegates, he said, worried about the possibility of PNHA domination of local groups. "We don't want our own organization to be PNHA Local 689. Still, it's necessary to have a strong national association." And the moderate, quiet-mannered Dr. Fink expects his hospital to have a delegation at the National Assembly meeting next spring.

Even well-established and well-organized house officers' groups may have to perform some continuing physicians' unionism education on their members. Said Dr. Ian V. Jones of the strong and prestigious Association of Fellows at the Mayo Clinic: "I foresee no prob-

lems other than those at any house staff organization in the Midwest. We'll have to vote on it, and I don't know which way the vote will go." But Dr. Jones did vote for unionization—which may be significant, since he is also alternate delegate to the American Medical Association from that group's Interns and Residents Business Section, and plans to run for delegate (with PNHA backing) this year.

Some National Assembly delegates see no need for collective bargaining, or any sort of adversary relationship, with their training institutions. "We have a fantastic setup at Akron General Hospital, and we don't need the PNHA there," said perky Dr. Jess Szilva. "Everything we've asked for, we've gotten. We've gotten due-process rights just out of meeting with the administration. We've gotten better on-call facilities just by complaining. We expect to get a raise this year out of our discussions. The hospital even paid for me to come here."

"We haven't needed things written down. And what we want most of all is to keep the status quo."

Still, Dr. Szilva supports the PNHA, whether as a coordinating group or as a union. "I don't know if we'll be able to," she said, "but I'd like to keep our membership."

Obvious Step

For those who are already organized as collective bargaining units, the PNHA's becoming a union was only an obvious step, and they don't expect too much for themselves. "It'll only be minimal help, at least at the beginning," contended Dr. Irwin Abraham of New York City's tough Committee of Interns and Residents, whose huge delegation had more than 40 votes. "The PNHA will continue to present house staff views at the national level. But the biggest help it'll be to us will be its organizing house staff in the areas surrounding New York, so they won't want to join the CIR and dilute us with small, weak groups."

PNHA president Harmon is a little less sanguine than are some of his delegates. "We'll lose some of the smaller house staff associations, the ones that were only in it for information, where they paid \$60 in dues to send one delegate even though they had 20 members," he predicted. "But the new constitution has a full-membership provision—all our members will now have to pay dues for all their members, not just for the minimum number. So we'll have a net gain in PNHA membership."

"We've outgrown our role as a coordinating and facilitating organization," he continued. "Now we're going after the people who are committed—completely—to the PNHA." The tall, slender PNHA president believes that by next spring's National Assembly meeting, somewhere on the West Coast, his organization will have between 10,000 and 12,000 dues-paying members.

One problem troubles the PNHA leadership. Though some 12 house staffs filed for recognition as collective bargaining units with the National Labor Relations Board last spring, the four-man board—short one member—

is reportedly deadlocked as to whether house officers can organize under federal legislation and, if so, whether they can have their own union or must join with full-time attending physicians.

Up in the Air

As a result, the membership provision of the new constitution remains up in the air. Two articles concerning membership passed the National Assembly, one restricting the organization to house officers, the other opening it to the attendings, just to be prepared. But the question arises, what if the NLRB rules, as the Association of American Medical Colleges contends, that interns and residents are students and not employees, and therefore not permitted to organize?

"Well, it won't change much," said one PNHA officer. "We'll still have our new constitution and our membership strength. Many of our local affiliates are organized as unions under state law, and that won't change. Maybe we'd even pick up some affiliates, because a ruling like that would really get house staff mad."

AMA Relations to Continue

The PNHA National Assembly decided, by a two-to-one vote, to continue its present relations with the AMA. The decision, hotly debated in reference committee and on the floor of the assembly, means that the PNHA will continue to endorse—and elect—the officers of the AMA's Interns and Residents Business Section.

However, the new resolution makes explicit what has previously been an open secret. According to the measure the delegates passed, the IRBS "shall be considered as a committee within the PNHA structure." Furthermore, it requires that "the IRBS be totally accountable to the PNHA and procure the approval of the PNHA before deciding any appointments or public statements."

The strong resolution, introduced by PNHA vice president Asimus, turned back a measure by the CIR's Dr. Richard Cooper that would have cut off any relationship between the PNHA and the IRBS. His resolution defeated, Dr. Cooper then turned around and accepted PNHA endorsement for the secretaryship of the IRBS.

No Scholarship Trade-Off

Delegates also emasculated a resolution putting the PNHA on record as supporting the idea of scholarships from the federal government in return for a period of service in medically underserved areas of the country. In knocking these provisions from the PNHA health manpower legislation statement, the delegates disavowed their president's congressional testimony last spring in favor of a bill containing such a trade-off for medical students.

Finally, the National Assembly decided to take no stand at this time on national health insurance. Instead, they referred a resolution that would have endorsed universal mandatory coverage, with no co-payments or deductibles, to committee to study the matter and report back next spring.

Studying Uric Acid



Caltech chemist Dr. Neil Mandel adjusts the goniometer of an X-ray diffractometer he used to elucidate the structure of uric acid crystals causing gouty arthritis.

Nose Drop Route Improves Action Of Synthetic LHRH

Medical Tribune World Service

BRATISLAVA, CZECHOSLOVAKIA—The short duration of action of injected synthetic luteinizing hormone releasing hormone (LHRH), which has limited its use in diagnosing anterior pituitary incompetence and in producing ovulation in sterile and/or anovulatory women, can be overcome by changing the method of administration, a British Investigator reported at an International Symposium on Human Reproduction here. Dr. W. R. Butt, of the department of clinical endocrinology, Birmingham and Midland Women's Hospital, Birmingham, England, said that the decapeptide can be self-administered by the patient as nose drops.

When LHRH is taken as nose drops, only about one-tenth of the dose is absorbed. However, the equivalent parenteral effect is obtained by increasing the dose by a factor of ten, Dr. Butt said.

In diagnostic applications, the patient can herself, at home, maintain constant LHRH levels for several days before reporting for pituitary function tests. In therapeutic applications, the patient can self-administer the drug and follow basal body temperatures so as to determine the optimal time for coitus.

A further possibility has arisen with the development of an analog of LHRH which has been shown in patients to be four times as potent as the natural decapeptide, with three to four times the biologic half-life of the parent molecule, Dr. Butt said. By combining nose-drop administration with the new analog, once or twice daily self-administrations should maintain maximum releasing activity.

The Only Independent Weekly Medical Newspaper in the U.S.

Medical Tribune

and Medical News
Published by Medical Tribune, Inc.

A Sleeping Giant Awakens...

TODAY, AFTER A LONG PERIOD of silence, medical organizations are finally standing up and speaking out for the rights of patients and the patient-physician relationship.

At long last, the American Medical Association recognizes that the medical profession must shoulder an extension of its historic responsibility—the protection of the patient not only physically and medically, but socially and personally as well. The A.M.A., long a sleeping giant, has finally awakened and added its voice to those of indi-

vidual physicians, research scientists and other organizations in the fight to preserve patients' rights and the physician-patient relationship. In just a period of months, the A.M.A. has undertaken two court actions—one on review of the patients' right to hospitalization, and more recently on the so-called Maximum Allowable Cost (MAC) regulations of the F.D.A. These actions are to be commended. They should serve as a continuing precedent of vigilance in protection of patients' rights and the physician-patient relationship.

...To Fight for Rights Is Not Futile...

TO STAND UP against "the government" and fight its impingement upon the rights of our patients and our rights as physicians is, thank heavens, not futile in our society. It is effective. Its effectiveness is attested by victory after victory when issues are finally joined. The Committee on the Cure of the Diabetic has successfully fought a five-year battle for the physicians' rights in treating his diabetic patients. The Empire State Physicians Guild has so far successfully challenged the use of triplicate prescriptions identifying patients receiving psychoactive medications in New York State. Most significantly, in this case, physicians were joined in the court action by the New York Civil Liberties Union.

One must commend the New York Civil Liberties Union for addressing

this issue. Some years ago when the government was first infringing upon the rights of scientific investigators to study hallucinogenic agents in animal research under conditions inconsistent with academic freedom, the A.C.L.U. did not choose to join the issue. Government infringement of the rights of science was soon followed by its invasion of the rights of both physicians and patients.

All organizations truly devoted to the rights of individuals, all scientific bodies concerned with a free science, all official bodies of medicine seeking to protect the rights of patients would do well to study carefully the sequence of events which follows a lack of vigilance and that which follows a vigorous struggle for human rights.

...Ironie

IT IS IRONIC that the defense of rights of individual patients in medical matters has now, as a last resort, become a legal matter. It is also ironic that when the issues are clearly defined our courts have repeatedly "slapped down" governmental invasion of patient privacy

and other human rights. This is the time for physicians—inside of government as well as outside—to join with their colleagues in recognizing and setting upon the principle that you cannot protect patients by destroying their precious rights. A.M.S.

More on Federal Interventions

THE OCTOBER 17 ISSUE of Science contains an editorial devoted to the problem of federal intervention in universities. It notes that since the late fifties when "federal grants started to become a substantial factor in university budgets," government interference in academia has burgeoned so that "the universities are now forced to cope with laws, proposed laws, regulations, proposed regulations, and authority-grabbing bureaucrats."

The Science editorial laments that although the laws are proposed and enacted for worthy purposes, their impact on the financial and intellectual

life of the universities is severe. "For severe," read "deplorable." It terms ironic that a "government which is unable to manage its own affairs competently insists on spreading its own brand of inefficiency throughout higher education."

The final sentence states that "A truly unified academic community could halt the federal crippling of higher education." Note that the message of the leading editorial on this page calls on physicians to unite to halt the crippling effects of federal and other governmental intervention in many aspects of medical care. A.M.S.

The Mortality of Diabetics

CLINICAL QUOTE: "The mortality ratio of the poorly-controlled diabetics was approximately two-and-a-half times that of the well-controlled cases, indi-

cating that control is an important factor in the mortality of the diabetic." (Dr. George Goodkin, citing a major finding of a 20-year insurance study.)



"I think my dog has run off with another man."

© 1975, Medical Tribune, Inc.

LETTERS TO TRIBUNE

'Absurd Law'

I wish that you elaborate on this wonderful Manhattan Federal Court that reinstated the privilege of patients (MT, Sept. 3).

So that does eliminate the absurd law that New York State enacted whereby every prescription of the so-called "dangerous" drugs should be made known to the state authorities.

It seems also that this ruling may benefit patients all over the land, where you have state inspectors going behind the pharmacist's counter to see, suspect and decide if the nature or frequency of prescriptions written in the judgment of the physician fits with their own convictions. Was not [the late] Narcotics Commissioner Anslinger who said once that an action of this kind by narcotics agent will draw a mandatory sentence of three years?

Thank you for your good reporting.
HENRI RATILE, M.D.
Mobile, Ala.

Malpractice Service

I read with dismay the letter of Dr. Sidney A. Bernstein (MT, Sept. 24) ... Dr. Bernstein accused me and my service of contributing to the malpractice problem. This allegation arose from a foundation of ignorance, for Dr. Bernstein has no understanding of the nature and function of our organization, nor did he bother to inquire.

RONALD E. GOTS, M.D., PH.D.
Medical Director
National Medical Advisory Service
Washington, D.C.

Not a book review, Book Blospy extracts from the book itself a few quotations to show its character.

Rheumatology: An Annual Review. Vol. 6, Immunological Aspects of Rheumatoid Arthritis. Series Editor: J. Rotstein. Volume Editors: J. Clot, J. Sany. Published by S. Karger.

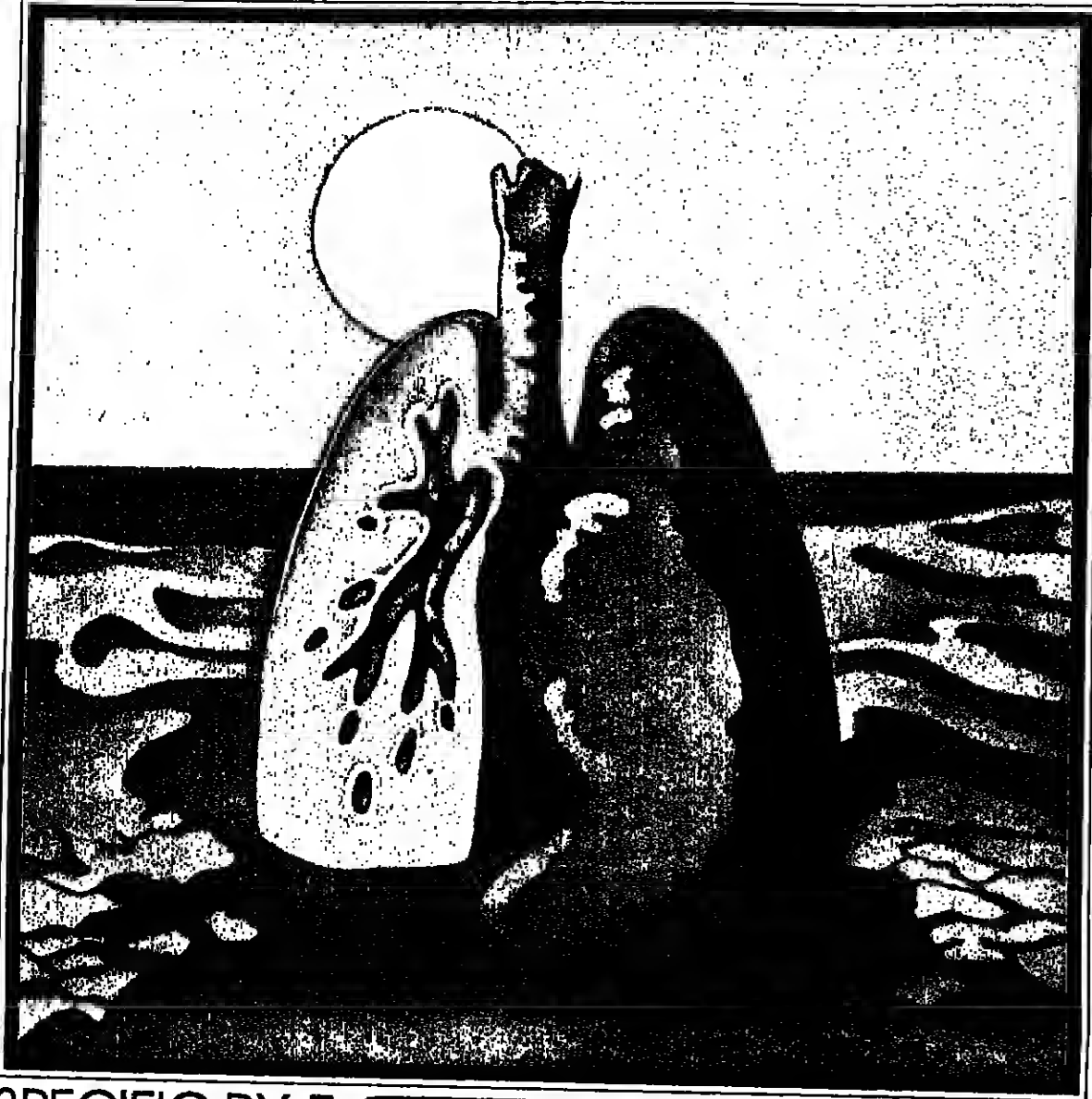
"...evidence has been gathered indicating that rheumatoid arthritis is closely associated with immunological abnormalities. The infiltration of synovial membrane with mononuclear cells, including plasma cells synthesizing immunoglobulins, the formation of lymphoid aggregates in the synovium and an ever increasing number of abnormal immunological findings have served to sustain and to strengthen the now common view that immunopathological processes directly underlie the develop-

ment of joint lesions in this disease. "...an International Symposium on Immunological Aspects of Rheumatoid Arthritis was held in Montpellier (France) from 28 to 30 March 1974. Sponsored by the 'Société française de Rhumatologie' and the 'Institut national de la Santé et de la Recherche médicale', this meeting grouped more than 200 workers from 20 countries.

"It was organized into six sessions on the main topics of immunopathology of rheumatoid arthritis: immune complexes and complement, cell-mediated hypersensitivity, antinuclear factors, macrophages B and T cells, experimental immunological models and infectious agents.

"This book consists of material presented during the symposium and is meant for a review of more recent immunological data concerning rheumatoid arthritis."

SPECIFIC SYMPTOM: NONPRODUCTIVE COUGH



SPECIFIC RX: **Hycotuss** EXPECTORANT

Because specific symptoms require specific therapy, Hycotuss® Expectorant was formulated to specifically treat nonproductive cough associated with respiratory tract congestion.

Hycotuss® Expectorant contains hydrocodone bitartrate, a highly effective antitussive, and glyceryl guaiacolate which acts to liquify and dislodge viscous secretions in the bronchi.

Relieves persistent coughing while it helps liquify bronchial secretions

Usual Dosage:

Adults 1 teaspoonful every four hours, after meals and at bedtime.

Children (Over 12 years) same as adults. (2 to 12 years) ½ teaspoonful every four hours and at bedtime.

Note: Telephone Rx's may be refilled 5 times within 6 months. Telephone Rx's permitted in most states.

DESCRIPTION Each teaspoonful (5 ml) contains:

Hydrocodone bitartrate..... 5 mg
Glyceryl guaiacolate..... 100 mg
Alcohol U.S.P. 10% v/v

Hydrocodone is 7, 8-dihydrocodeine, a derivative of codeine.

ACTIONS Hydrocodone is a centrally acting narcotic antitussive providing cough relief for up to 8 hours. Glyceryl guaiacolate acts as an expectorant by producing a less viscous excretion thereby facilitating its expulsion.

INDICATIONS Indicated for the symptomatic relief of coughs. Especially useful in unproductive coughs associated with upper and lower respiratory tract congestion.

CONTRAINDICATIONS Hycotuss® Expectorant should not be used in patients with hypersensitivity to hydrocodone or glyceryl guaiacolate.

WARNINGS Hycotuss® Expectorant should be prescribed and administered with the same degree of caution appropriate for the use of other oral narcotic-containing medications since it can produce drug dependence and, therefore, has the potential for abuse. Patients should be warned not to drive a car or operate machinery if they become drowsy or show impaired mental and/or physical abilities while taking Hycotuss® Expectorant. Patients receiving narcotic analgesics, phenothiazines, other tranquilizers, sedative-hypnotics or other central nervous system depressants (including alcohol) concomitantly with Hycotuss® Expectorant may exhibit an additive central nervous system depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS Before prescribing medication to suppress or modify cough, it is important to ascertain that the underlying cause of cough is identified; that modification of cough does not increase the risk of clinical or physiologic complications, and that appropriate therapy for the primary disease is provided.

ADVERSE REACTIONS Adverse reactions, when they occur, include sedation, nausea, vomiting and constipation.

DOSEAGE AND ADMINISTRATION Hycotuss® Expectorant should be taken after meals and at bedtime, not less than 4 hours apart. Treatment should be started with the suggested initial dose and subsequent doses adjusted if required.

Usual Dosage

	SYRUP Teaspoonful (5ml)	Maximum single dose
Adults	1	3
Children over 12 years	1	2
2 to 12 years	½	1

Under 2 years Dosage should be calculated on Hydrocodone, 0.5 mg/kg/24 hrs., divided into four equal doses.

DRUG INTERACTIONS The central nervous system depressant effects of Hycotuss® Expectorant may be additive with that of other central nervous system depressants.

MANAGEMENT OF OVERDOSE Signs and symptoms: Serious overdose with Hycotuss® Expectorant may be characterized by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdose, apnea, circulatory collapse, cardiac arrest and death may occur.

See Brief Summary for prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, New York 11530

Early Repair of 'Dashboard Knee' Prevents Arthritis

Continued from page 8

Nagel said. "Even with high forces, the knee would occasionally receive only a bruise, while a fracture of the femur, or dislocation of the hip, would be the more serious pathology."

"If the knee impacted a rigid steering column support, a sharp edge of the radio, or an instrument panel knob, there might be a laceration, or a fractured patella."

When forces were applied to the knee from several directions simultaneously, the result was a fracture of the tibial plateau. For example, "The knee of one occupant sustained a tangential force and was trapped under the dashboard, while at the same time it sustained an axial force from a buckling floorboard, producing minor displacement of the medial plateau. . . . In two of our younger patients, tears of the posterior cruciate ligament occurred when major force was applied perpendicularly in an anterior-posterior direction to the proximal tibia."

Sports Cars

Another problem, especially in sports cars, is trapping of the leg below the dashboard, with hyperextension of the knee from the contact while the body is going toward the windshield. This may also tear the posterior capsule and cruciate ligament. If, in addition, the legs or upper body are rotated, "valgus or varus strains are produced which can injure the structures on the medial or lateral side of the knee."

Two of four severely-injured knees and one classified as mild showed degenerative arthritis on follow-up one-and-a-half to five years postincident, Dr. Nagel continued. The "mild" injury, however, may have been more severe than originally believed.

Automobiles should be equipped with "a) a broad deformable, lower dashboard that the right front seat passenger's legs could not slip under; and b) lower dashboard padding to provide protection against a second collision of the driver's knees against a rigid steering column support, or sharp object under the dashboard," Dr. Nagel suggested. "While seat belts should be worn, some car occupants suffered knee injury despite their use, either because they were applied too loosely or because they stretched on impact. One severe knee injury also occurred to a belted passenger when the force of the collision pushed the dashboard back against the knee."

Circumcision No Help

Medical Tribune Report

EVANSTON, ILL.—Finding no evidence that circumcision prevents penile or prostate cancer or lowers the incidence of VD, an American Academy of Pediatrics task force has concluded circumcision is not essential to adequate total health care. "A program of education leading to continuing good personal hygiene would offer all the advantages of routine circumcision without the attendant surgical risk," says the AAP.

FDA Chided for Withholding Anti-Asthma Steroid Aerosol

Continued from page 1

not augment systemic steroid levels or suppress endogenous cortisol.

In the latest report by the British multi-center group, the use of inhaled steroids by 75 patients who were starting long-term corticosteroid therapy for the first time was shown to "control asthma as well as did oral prednisone." In contrast with the 30 per cent incidence of systemic effects in patients on oral prednisone, the only side effect in the group using the inhalants was a 5 per cent incidence of symptomatic oropharyngeal candidiasis. There was no evidence of fungal colonization of the bronchial tree, the British team said in its report in *Lancet*, September 13, 1975.

As Good as Prednisone

"By both the subjective and objective criteria used in the assessment of the control of asthma, both inhaled beclomethasone dipropionate or oral betamethasone valerate did as well as the standard drug, prednisone," the investigators reported. The studies have shown that a daily dose of 400 micrograms of inhaled drug was approximately equivalent to 7.5 mg. daily of prednisone.

Overall, 18 per cent of the patients in the prednisone group had to be withdrawn from the trial because of unwanted systemic effects, and another 15 per cent experienced side effects that were not severe enough to warrant withdrawal. In contrast, only one patient on inhaled corticosteroid was withdrawn, because of edema and an increase in weight.

Systemic Steroids Also

The British group stressed, however, that in the management of asthma exacerbations, systemic steroids will usually be needed as a supplement to aerosol therapy.

Dr. Clark said the drug's mode of action appears to be "very much a surface activity, as judged by the vasoconstrictive effect when it is applied to a subject's skin. The high surface action means that the dose can be delivered effectively to the lungs. What is absorbed in the GI tract is metabolized."

"Our present information suggests that the drug's limitations as a steroid in asthma management are that it can't be used in high doses or in status asthmaticus," he continued. "It's thought that, in status, the airway obstruction is so bad that the aerosol won't get into the lungs. Its most valuable role, currently, is as a systemic steroid-sparing agent. Patients on high doses of steroid can be brought to a range where the systemic side effects are reduced. In others, it can replace oral therapy entirely."

The British expert politely chided the Food and Drug Administration for what he saw as undue prudence in delaying approval of beclomethasone.

"Hopefully, with the widespread use of beclomethasone in the rest of the Western world—as well as the English-speaking Pacific nations—the F.D.A.

should come to a speedy conclusion as to its efficacy," he declared. "It has been reviewed and approved by the regulatory agencies of the U.K., Australia and Canada, to name only some, and there should be enough evidence on which the F.D.A. can base a judgment. If not, the F.D.A. ought to advise the other regulatory agencies what to look for, because the F.D.A.'s hesitation suggests that the other agencies have been remiss in some important respects."

The drug was developed by Allen & Hanbury Research Ltd., England.

Therapists Allay Children's Anxieties



"Child life" therapists, such as Lurinda Mollahan, shown above comforting three-year-old traffic accident victim Troy Shrum, help allay anxiety and apprehension in pediatric patients hospitalized at the Health Sciences Center, University of Oregon, Portland, through supportive daily visits. The therapists are not nurses but are assigned to the nursing staff.

Medical Tribune

Next Slide, please

Singing for sexual liberation

page 29

Pediatricians rate sex education for teens

page 35

October 15, 1975

Clifford J. Sager, M.D.

watch for the November 19 issue of sexual medicine today

confidentiality and the teen-age girl—15-year-old Suzanne is pregnant. You've just told her so. "Don't tell my parents," she begs, "they'll murder me. Anyhow, I'm getting an abortion so they won't ever know. Won't they? Should they? As the attending physician, what would you do? Are you anxious about your own confidentiality and reputation in your community?"

the problem of treating homosexuality—Despite greater toleration of homosexuality as a variant life-style, physicians are sometimes consulted by homosexual patients seeking to reverse their orientation. Dr. Samuel B. Hadden candidly shares his pioneering methods—from positive one-to-one transference to group dynamics to heterosexual commitment in 95 per cent of the patients he treats.

moving toward orthodoxy in the name of love

The distinguished Dutch sexologist Dr. Jan J. B. van Kesteren explains why orthodox physicians are reluctant to treat more requests for help with sexual problems. He discusses the importance of the physician's attitude in the treatment of sexual problems.

On Barbara for Women New York and his wife marriage. It provides for and a frequent Mrs. Bell first model magazine, 1975.

Because this provocative discussion, already seen by millions in its first run, may ease the problems of physicians in talking with patients about sexual and marital relationships—patients who may bring up questions and attitudes shown on this program—Medical Tribune is presenting highlights of the Barbara Walters

children, willing to talk about their "adulterous life?" Howard: We are very open about it . . . and it seemed as natural as talking to our friends to come on [TV] since you asked us. Later on, Howard said: I would say, simply and honestly, we're doing what thousands, millions of people are doing.

interview and its ramifications that had already been covered in volumes seems a bit unfair. It would be most easy to simply play the devil's advocate and say, "I think, perhaps, the fallings of the relationship that Howard and Christina present in

continued on page 15

Current Opinion

The Importance of Being Earnestly Critical

A Follow-Up Report on the Effect of Treatment of Diabetes on Cardiovascular Disease

By DR. RICHARD GUNNER
Clinical Professor of Medicine
State University of New York Downstate Medical Center, Brooklyn
Associate Editor, MEDICAL TRIBUNE

THE UNRESOLVED Great Diabetes Polemic might well be an appropriate substitute designation for U.G.D.P., abbreviation for the University Group Diabetes Program. Since the report first appeared in 1970, there has been continuing criticism and controversy concerning the design of the trial, validity of the data, significance of the conclusions, manner in which the findings were presented to physicians and public, ethical questions of bias potentially prejudicing the report, and proposed F.D.A. regulatory strictures on the hypoglycemic agents studied, specifically tolbutamide and phenformin—with even broader regulatory scope in prospect.

The five-year travail has eclipsed the trial itself, which was designed to evaluate "the effect of hypoglycemic agents on vascular complications in patients with adult onset diabetes." All of this has created a climate of confusion for the clinician and has left him without clear guidelines in treating diabetic patients.

As stated in a recent editorial by Dr. Sol Sherry in another context (*New Eng. J. Med.* 293:300, Aug. 7, 1975), "No therapeutic trial has escaped adverse criticism... at issue, as in all therapeutic trials, is the probability of the accuracy of the conclusion." The accuracy of the conclusion that hypoglycemic drugs have an adverse effect on cardiovascular mortality was first challenged by this writer, largely on the basis of the paucity of the U.G.D.P. data (*Current Opinion, MEDICAL TRIBUNE*, Sept. 7, 1970). Controversy experience was cited from a much larger insurance-mortality investigation at the Equitable Life Assurance Society of the U.S. (Goodkin, G., Wolloch, L., and Gunner, R., *Diabetes* 16:525, July, 1967). The Equitable Life study has now been updated by Dr. Goodkin (*Mortality Factors in Diabetes—A Twenty Year Mortality Study, J. Occup. Med.* 17: 716, Nov., 1975). This comprises by far the most extensive investigation of prognostic factors in diabetes ever carried out. The study includes all diabetics, numbering 10,538, who applied for insurance at the Equitable between the years 1951-1970, with a total of 1,478 deaths. No increase in deaths due to cardiovascular disease was observed in diabetics receiving hypoglycemic drugs compared to those managed with diet alone. Accordingly Dr. Goodkin concludes, "Our data are at variance with the findings of the U.G.D.P. program."

Other New Studies Controversy U.G.D.P. Findings

AT THE RECENT annual meeting of the American Diabetes Association in New York City this June, Drs. S. Carlstrom, G. Persson and B. Schersten of Lund, Sweden, presented a study titled "Anti-diabetic Treatment in the Prevention of Cardiovascular Disease of Subjects with Borderline Glucose Tolerance." Their investigation comprised an eight to 10 year follow-up of 578 subjects divided at random into four groups: no treatment, diet, diet-placebo,

and diet-tolbutamide (1.5 grams daily). The incidence of cardiovascular complications developing in this prospective clinical trial was as follows:

No treatment	30 per cent
Diet only	21 per cent
Diet-placebo	23 per cent
Diet-tolbutamide	14 per cent

These figures compare with 6 per cent developing cardiovascular disease in control subjects. The Swedish investigators conclude, "Judging from our results, borderline diabetics have a higher frequency of cardiovascular complications than controls, and anti-diabetic treatment of borderline diabetics may prohibit and postpone the development of cardiovascular damage." This report directly contradicts the U.G.D.P. findings, and it merits careful analysis as the full data become available.

No Adverse Effects

Another investigation which has been newly updated to provide an eight-and-a-half-year follow-up is that of Dr. Harry Keen of the University of London and Director of Metabolic Medicine at Guy's Hospital. His earlier report on long-term treatment with tolbutamide (1 gm. daily) administered to 248 borderline diabetics in a placebo-controlled, randomly-allocated, double-blind study had shown "no hints of adverse effects in respect of total mortality, of mortality attributed to cardiovascular cause or of mortality attributed to coronary artery disease." (Keen, H. et al, in *Early Diabetes*, Ed. by R. A. Cameron-Davalos and H. S. Cole, Academic Press, N.Y. 1973, p. 571). His current survey, presented this August in Washington, shows significant advantage to the tolbutamide-treated group in respect to cardiovascular complications, i.e. angina, infarction, development of electrocardiographic abnormalities. He decided that the findings in the eight-and-a-half-year analysis supported the conclusions regarding "possible beneficial effects of tolbutamide and absence of adverse effect, drawn from earlier analyses."

Dr. Keen reported similar findings in a group of 204 civil service patients treated with phenformin (50 mg/day timed disintegration capsules) or with similar placebo capsules. In a five-year follow-up, "there were significantly fewer events of non-fatal myocardial infarction in the phenformin than in the placebo group (3.3 per cent vs. 10.4 per cent) and also a significant lower frequency of Minnesota-codable electrocardiographic deteriorations (17.4 per cent vs. 31.8 per cent)." No elevations in blood pressures were observed in the phenformin treated subjects as reported in the U.G.D.P. study.

Dr. Keen concludes, "We are not alone in finding indications that the oral antidiabetic drugs subjected to trial (tolbutamide and phenformin) offer significant advantage compared with placebo. Nor are we alone in failing to confirm the adverse effects reported by the U.G.D.P." He observes further, "Our findings are in accord with all other published findings from controlled, double-blind, random-allocation, prospective trials of the substances, with the single exception of the mortality findings of the University Group Diabetes Program."

Is Control of Blood Sugar Worthwhile? Newer Concepts

THE PURPOSE and controversial adverse cardiovascular effects of the oral hypoglycemic agents have obfuscated the stated primary purpose of the U.G.D.P. study, namely to test "the hypothesis that blood glucose control delays or prevents the development of vascular complications in patients with diabetes.... The results of the U.G.D.P. ... did not demonstrate a beneficial effect associated with variable degree of lowering of blood glucose by any of the hypoglycemic agents considered." (University Group Diabetes Program) *Diabetes*, 24:65, Suppl. 1, 1975.

Is it then futile to attempt to control the blood sugar level, which has been the keystone of therapy in diabetes since, and even before, the discovery of insulin? When the oral hypoglycemic sulfonylureas were introduced in the nineteen fifties they gave promise of being the greatest advance in the treatment of diabetes since the advent of insulin thirty years earlier. And when it developed that tolbutamide and other sulfonylureas sensitized the pancreatic beta cell enhancing release of insulin, a physiologic rationale for their use appeared established. Accordingly, the U.G.D.P. report that patients on tolbutamide fared worse than those on insulin appeared inexplicable, since the action of tolbutamide appeared to be mediated through insulin. The inference could be drawn, as indeed it has been, that insulin itself contributed to atherosclerotic complications of diabetes. Why the biguanides, i.e., phenformin, should also have an adverse effect on cardiovascular mortality, as per the U.G.D.P. findings, would be further enigma. Phenformin, like tolbutamide, lowers blood sugar, but by a different mechanism, which appears due in considerable measure to inhibition of glucose absorption from the gut. The common denominator of these differently acting agents, as well as insulin, is to lower blood sugar.

Control Essential

Blood sugar and insulin are no longer the focus of interest and research in the rapidly expanding knowledge and concepts of diabetes. Nonetheless, newer developments have only reaffirmed that control of hyperglycemia is essential not only in the acute manifestations of diabetes as has long been recognized, but also in helping prevent degenerative complications such as angiopathy. Whether angiopathy and other degenerative lesions are due to the recently elucidated sorbitol pathway or hormonal factors such as hypersecretion of growth hormone as has also been suggested, the newer concepts implicit-

Dr. Squibb's Scarifier



Brass and steel scarifiers, like the one above owned by Dr. E. R. Squibb and now in the Squibb Museum, Princeton, N.J., were used in the mid-1800s for smallpox inoculations. The 12 double-edged lancets of the egg-sized scarifier adjusted to graze the skin or cut 3/16 inch deep.

ly and explicitly dictate control of blood sugar.

Writing for the American Heart Association's publication, *Modern Concepts of Cardiovascular Disease* (43: 103, August, 1974) Dr. Knud Lundback of Aarhus University, Denmark, states, "All the available evidence from acceptable clinical and experimental study indicates that 'good diabetes control' inhibits to some degree the development of diabetic microangiopathy. Complete control—meaning normal blood sugar hour by hour, between meals, each day of life—might perhaps prevent diabetic microangiopathy entirely, but in practice this is very rarely possible, if ever.... Good diabetes control probably inhibits the development of a diabetic macroangiopathy, but too little attention has been directed toward the problem to make any definite statement possible.... Angiopathy studies have shown irregularities of large vessels to be correlated with blood glucose, while true obliteration is related to blood lipids."

Dr. Roger H. Unger of Southwestern Medical School, in presenting the Banting Memorial Lecture at the recent annual meeting of the American Diabetes Association, used no less treacherous terms in stressing the importance of controlling hyperglycemia: "Nature, through the coordinated secretion of insulin and glucagon, makes a formidable, and in most humans a remarkably successful, effort to avoid hyperglycemia throughout life. These humans virtually always escape microangiopathy, whereas those humans in whom nature fails in its efforts to avoid hyperglycemia usually develop microangiopathy."

In addition to inhibiting diabetic angiopathy, control of the blood sugar is important in preventing other degenerative lesions such as cataract formation in the lens and the widespread lesions of diabetic neuropathy. Dr. J. D. Ward and coworkers in a study at London's Guy's Hospital Medical

Continued on page 22

The Living Cadavers of Anatomist George Stubbs

IN 1732, WHEN THE TEACHING OF ANATOMY in English medical schools was poor and the dissection of specimens almost unknown, George Stubbs (1724-1806) was carrying out dissections and sketches of small animals on his own. He was eight years old at the time.

At 27, he had completed the eighteen etchings for Dr. John Burton's *Essay Towards a Complete New System of Midwifery*, including views of the female pelvis region, genitalia, embryos in situ, and various obstetric instruments. The collaboration was based on Stubbs' own human dissections, at a time when anatomists were considered grave-robbers, and obstetricians, known as "male midwives," were required for modesty's sake to wear women's clothing during deliveries.

In 1758, Stubbs began dissecting horses. It is said he could carry a

carcass on his back up a flight of stairs. With no antiseptics, he relied solely on cold weather and perhaps vinegar to prevent decomposition during the six to eight weeks of study on each specimen.

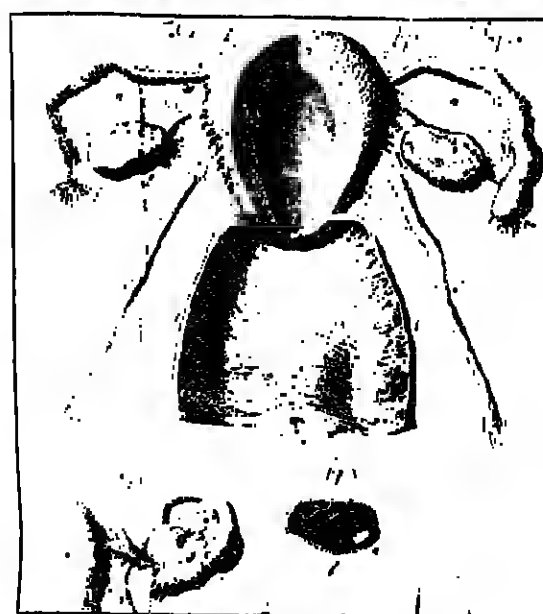
Stubbs' methods compare closely with those of Dr. Bernhard Siegfried Albinus, Professor of Anatomy and Surgery at Leyden, and author of the famous *Tabulae Sceleti et Musculorum Corporis Humani*, published in 1747. Both used grids of string on wooden frames placed at intervals from the subject to establish correct proportions, and both referred to a skeleton to correct for distortions inherent in dissection. The two anatomists also avoided labeling the finished drawings by provid-

ing a key of lettered parts.

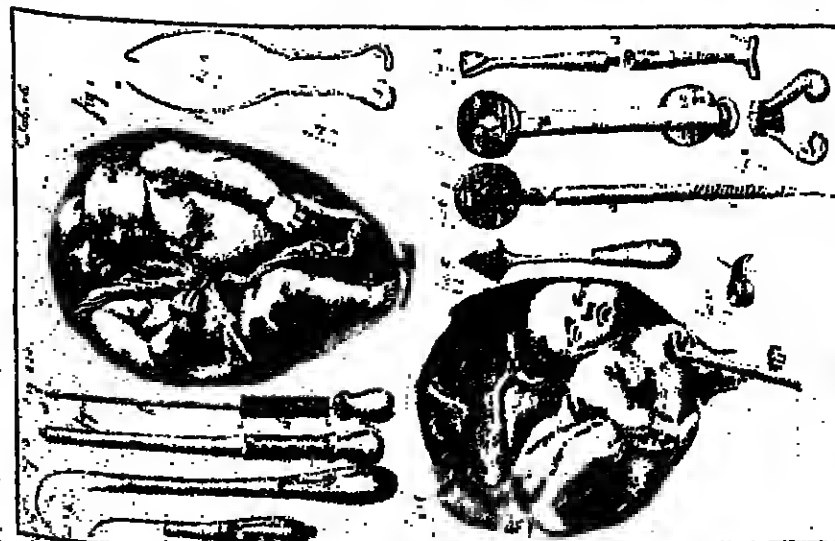
A *Comparative Anatomical Exposition of the Human Body with that of a Tiger and a Common Fowl* was Stubbs' last work and the consummation of his lifelong devotion to scientific anatomical representation. Like his friend Dr. John Hunter's great collection of prepared specimens and dissections, arranged to show developmental changes in various organs, Stubbs' comparative anatomy is clearly evolutionary in its intention.

The "living cadavers" shown here, along with scores of others, have recently been reproduced along with his texts in a large volume of *Anatomical Works*, published by David R. Godine, Boston.

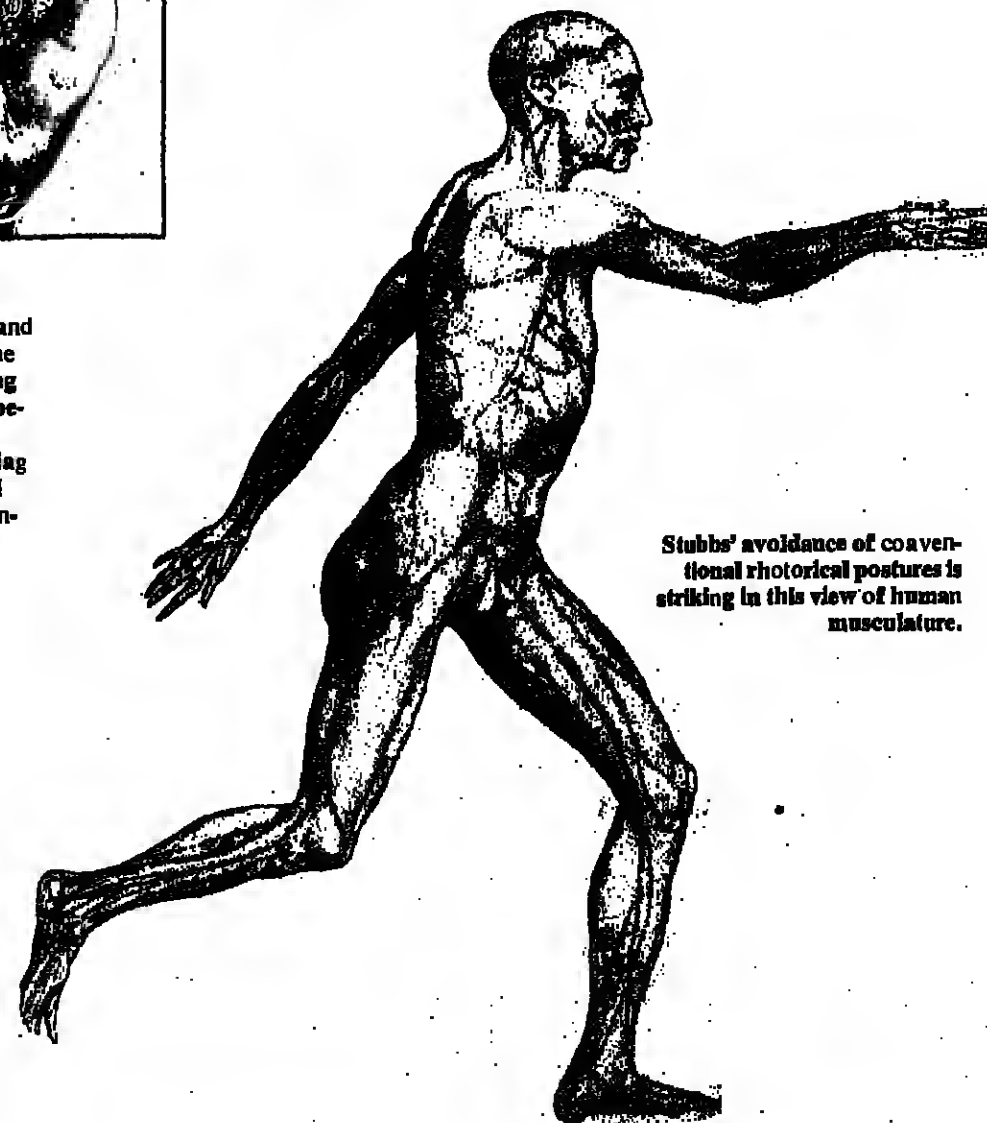
Diagram of internal female genitalia, partly dissected, with detail of Fallopian tube around ovary and a dissected ovary. Stubbs was 27 at the time.



Posterior view of human skeleton, left, shows Stubbs' accuracy of observation and his remarkable skill in demonstrating the curvature of the spine. Note also twisting of the radius over the ulna. Above and below, fetuses in utero, showing various faulty presentations, one of which is being corrected by an instrument. In crowded plate below, Stubbs records views of contemporary obstetric equipment.



Stubbs' avoidance of conventional rhetorical postures is striking in this view of human musculature.



Low incidence of diarrhea to date in clinical studies

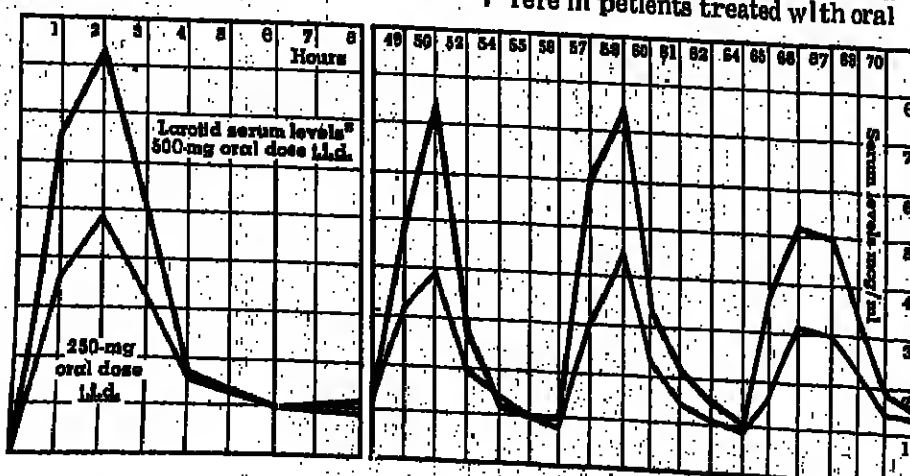
Absorption called the key








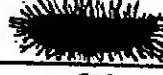

Because of its efficient absorption characteristics, high blood and urine levels of Larotid (amoxicillin) are rapidly achieved. Peak serum levels average 4.2 mcg/ml two hours after a single 250-mg oral dose and 7.5 mcg/ml one hour after a single 500-mg oral dose—both levels approximately twice as high as those obtained with equal doses of ampicillin.^{1,2}

Most of Larotid is excreted unchanged in the urine.² Average urinary excretion within 6 to 8 hours after oral administration ranges from 40 to 79% for the 250-mg dose and 59 to 79% for the 500-mg dose.^{1,3}

Hypersensitivity reactions can occur

As with other penicillins, it is anticipated that adverse reactions to Larotid (emoxiolillin) will be largely limited to sensitivity phenomena. While anaphylaxis is rare in patients treated with oral



GRAM-POSITIVE	
Alpha-hemolytic streptococci	
Beta-hemolytic streptococci	
<i>Streptococcus faecalis</i>	
<i>Diplococcus pneumoniae</i>	
Nonpenicillinase-producing staphylococci	
GRAM-NEGATIVE	
<i>Haemophilus influenzae</i>	
<i>Escherichia coli</i>	
<i>Proteus mirabilis</i>	
<i>Neisseria gonorrhoeae</i>	

In vitro bactericidal activity

Note: Because Larotil (umoxicillin) does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria such as resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Enterobacter* are resistant.

penicillins, the possibility must nevertheless be kept in mind. Larotid is contraindicated in patients with a history of penicillin hypersensitivity. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT** (See Warnings section of complete product information, a summary of which appears at right.)

**Efficacy demonstrated
in many infections**

Amoxicillin has been administered successfully to patients with a wide range of commonly seen infections due to susceptible organisms.* Over-all clinical evaluation of amoxicillin therapy was considered a "success" or "improvement" in 1267 of 1850 evaluable cases (68.5%).†

Ages of the 1860 patients studied ranged from under one year to over 80 years. Larold capsules were administered to 800 patients and oral suspension to the remaining 550. Dosage of the capsules ranged from 250 mg t.i.d. (the most frequently used dosage) to a single 8-Gm dose for the treatment of acute uncomplicated gonorrhea. Dosage of the oral suspension ranged from 50 mg t.i.d. to 250 mg t.i.d., with 125 mg t.i.d. the most frequent. The majority of patients were treated from seven to 10 days. A breakdown by type of infection follows:

Otitis Media: The pathogens most commonly isolated were *Diplacoccus pneumoniae* and *Hemophilus influenzae*. Of 180 cases with this diagnosis, 127 (98%) were ruled as a "success" or "improvement" after treatment with Larotid (amoxicillin).

Streptococcal Sore Throat: A success rate of 86% (174 of 202 cases) was observed with Laredo against the responsible pathogen, beta-hemolytic streptococci.[†] The great majority of the 202 patients in this group were children who received the oral suspension.

Other Upper Respiratory Infections: Beta-hemolytic streptococci* were the offending organisms for most of the infections in this group, which were diagnosed primarily as pharyngitis, with some cases of tonsillitis and a few cases of sinusitis. A success rate of 82% (56 of 68 cases) was achieved with Larotid.

Lower Respiratory Infections: Treatment with Larotid resulted in "success" or "improvement" in all of the 42 cases in which *Diplococcus pneumoniae* was cultured. *Staphylococcus aureus* was also cultured in 26 of the 38 cases; Larotid showed "success" or "improvement" in 96% (26 of 28 cases). The most common clinical conditions were bronchitis and bronchopneumonia.

Urinary Tract Infections: Cystitis, pyelonephritis and asymptomatic bacteriuria were the most frequent clinical diagnoses in this group. Of the 404 cases evaluated, *Escherichia coli* was cultured in 308 cases and treatment with Luracid resulted in "success" or "improvement" in 284 cases (93%). *Proteus mirabilis* was cultured in 70 patients, with Luracid effective in 67 (96%).

Skin and Soft Tissue Infections: *Staphylococcus aureus* was cultured in 108 cases, with "success" or "improvement" in 104 (96%); while beta-hemolytic streptococci were cultured in 99 cases, with "success" in 97 (98%). Impetigo and abscess were the most frequent diagnoses.

Gonorrhea: Administered as a single 3-Gm oral dose, Larotid showed a success rate of 97% in both males (85 of 88 cases) and females (114 of 118 cases).

"Success" or "improvement" was determined by a combination of clinical and bacteriological criteria. In infections due to beta-hemolytic streptococci and *N. gonorrhoeae*, only successes were included.

Low incidence of side effects reported to date

During the clinical investigations with amoxicillin, all cases treated were evaluated for side effects. No side effects or laboratory abnormalities which would be considered unusual for a penicillin derivative were reported by any of the investigators.

In 2658 total courses of therapy with amoxicillin, therapy was discontinued in only 52 patients.

Drug-Related Side Effects Associated with Amoxicillin

Based upon 2658 courses of therapy: 1811 with the capsule and 847 with the oral solution 81%.

SIDE EFFECT	CAPSULES		SUSPENSION	
	#	%	#	%
Diarrhea	24	1.3	16	2.1
Nash	24	1.3	17	2.0
Nausea	7	0.3	1	0.1
Urticaria	8	0.4	2	0.2
Monilia	4	0.3		
Nausea/Vomiting	7	0.2		
Diarrhea/Nausea	3	0.1		
Vomiting	2	0.1	4	0.4
Ooziness	2	0.1		
Cold	2	0.1		
Nausea/Headache	2	0.1		
Nash/Urticaria	2	0.1	1	0.1
Esophageal Spasm	1	0.05		
Stomachache	1	0.05	1	0.1
Balching	1	0.05		
Drowsiness	1	0.05		
Balching/ Numbness/Tingling/Itching	1	0.05		
Fever/Itching	1	0.05		
Difficult Breathing	1	0.05		
Mucus In Pharynx	1	0.05		
Diarrhea/Urticaria	1	0.05		
Diarrhea/Vomiting	1	0.05	4	0.4
Ooziness/Headache	1	0.05		
Conjunctival Ecchymosis	1	0.05		
G.I. Bleeding	1	0.05		
Abdominal Cramps	1	0.05		
Diarrhea/ Rash	1	0.05	1	0.1
Rash/ Diarrhea/ Vomiting			1	0.1
Sore Tongue			1	0.1
Rash/Vomiting			1	0.1
TOTAL	102	5.6	52	6.1

(1.9%) because of drug-related side effects. Laboratory abnormalities possibly related to amoxicillin occurred infrequently.

In these studies, there was a low incidence of diarrhea reported with amoxicillin capsules—1.7% or 30 of 1811 patients. Especially noteworthy was the low incidence of diarrhea reported with amoxicillin oral suspension—only 2.8% or 24 of 847 patients, significantly less ($p < 0.05$) than the incidence of diarrhea with ampicillin oral suspension (5.3% or 16 of 282 patients).

In breaking down the over-all incidence of diarrhea by age groups, it was found that in the group from 0 to 1 (newborn and 1-year-old infants), 13 of 108 patients receiving amoxicillin and Larotid (amoxicillin) can therefore be expected to be considerably higher in the newborn and infant age groups than in older children, which is true of all antibiotics.

Usual Adult and Pediatric Dosages

INDICATION	STRAIN ISOLATED	ADULT DOSAGE	PEDIATRIC DOSAGE*
Infections of the ear, nose, throat	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, <i>H. influenzae</i>	250 mg <u>t.i.d.</u>	Oral Suspension: 20 mg/kg/day in divided doses <u>t.i.d.</u> Drops: Under 6 kg (13 lbs): 0.5 ml <u>t.i.d.</u> ; 6-8 kg (13-18 lbs): 1 ml <u>t.i.d.</u>
Infections of the lower respiratory tract	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, <i>H. influenzae</i>	500 mg <u>t.i.d.</u>	Oral Suspension: 40 mg/kg/day in divided doses <u>t.i.d.</u> Drops: Under 6 kg (13 lbs): 1 ml <u>t.i.d.</u> ; 6-8 kg (13-18 lbs): 2 ml <u>t.i.d.</u>
Infections of the genitourinary tract	<i>E. coli</i> , <i>Proteus mirabilis</i> , <i>Strep. fecalis</i>	250 mg <u>t.i.d.</u>	Oral Suspension: 20 mg/kg/day in divided doses <u>t.i.d.</u> Drops: Under 6 kg (13 lbs): 0.5 ml <u>t.i.d.</u> ; 6-8 kg (13-18 lbs): 1 ml <u>t.i.d.</u>
Infections of the skin and soft tissue	Streptococci, susceptible staphylococci and <i>E. coli</i>	250 mg <u>t.i.d.</u>	Oral Suspension: 20 mg/kg/day in divided doses <u>t.i.d.</u> Drops: Under 6 kg (13 lbs): 0.5 ml <u>t.i.d.</u> ; 6-8 kg (13-18 lbs): 1 ml <u>t.i.d.</u>
Severe infections, or infections caused by less susceptible organisms		500 mg <u>t.i.d.</u>	Oral Suspension: 40 mg/kg/day in divided doses <u>t.i.d.</u>
Gonorrhea, acute uncomplicated nongonorrheal and urethral infections (males and females)	<i>N. gonorrhoeae</i>	3 grams—single oral dose	

*Note: Children weighing more than 8 kg (18 lbs) should receive the appropriate dose of the Oral Suspension: 125 mg or 250 mg/5 ml. Children weighing more than 20 kg should be dosed according to adult recommendations.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Infections due to susceptible strains of the following gram-negative organisms: *H. influenzae*, *E. coli*, *P. mirabilis* and *N. gonorrhoeae*; and gram-positive organisms: streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinae-producing staphylococci. Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine causative organisms and susceptibility to amoxicillin.

Contraindications: In individuals with history of allergic reaction to penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH MORE FREQUENT FOLLOWING PARENTERAL THERAPY, ANAPHYLAXIS HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. MORE LIKELY IN INDIVIDUALS WITH HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE THERAPY, INQUIRE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF ALLERGIC REACTION OCCURS, INSTITUTE APPROPRIATE THERAPY. ALWAYS CONSIDER DISCONTINUANCE OF AMOXICILLIN. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. ADMINISTER OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, AS INDICATED.

Usage in Pregnancy: Safety in pregnancy not established.

Precautions: As with any potent drug, assess renal, hepatic and hematopoietic function periodically during prolonged therapy. Keep in mind possibility of superinfections with mycotic or bacterial pathogens; if they occur, discontinue drug and/or institute appropriate therapy.

Adverse Reactions: As with other penicillins, untoward reactions will likely be essentially limited to sensitivity phenomena and more likely occur in individuals previously demonstrating penicillin hypersensitivity and those with history of allergy, asthma, hay fever or urticaria. Adverse reactions reported are associated with use of penicillins: *Gastrointestinal:* Nausea, vomiting, diarrhea. *Hypersensitivity Reactions:* Erythematous maculopapular rash, urticaria. **NOTE:** Urticaria, other skin rashes and


seum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Discontinue amoxicillin unless condition is believed to be life-threatening and emenable only to amoxicillin therapy. **Liver:** Moderate rise in SGOT noted, but significance unknown. **Hemic and Lymphatic Systems:** Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, agranulocytosis. All are usually reversible on discontinuation of therapy and believed to be hypersensitivity phenomena.

Dosage: Ear, nose, throat, genitourinary tract, skin and soft tissue infections—Adults: 250 mg every 8 hours. Children: 20 mg/kg/day in divided doses every 8 hours; under 6 kg, 0.5 ml of Pediatric Drope every 8 hours; 6-8 kg, 1 ml of Pediatric Drops every 8 hours. Lower respiratory tract infections and severe infections or those caused by less susceptible organisms—Adults: 500 mg every 8 hours. Children: 40 mg/kg/day in divided doses every 8 hours; under 6 kg, 1 ml of Pediatric Drope every 8 hours; 6-8 kg, 2 ml of Pediatric Drope every 8 hours. Gonorrhea (acute uncomplicated anogenital and urethral infections)—Males and females: 3 grams as a single oral dose. NOTE: Children weighing more than 8 kg should receive appropriate doses of oral suspension 125 mg or 250 mg/5 ml. Children weighing 20 kg or more should be dosed according to adult recommendations.

Note: In gonorrhea with suspected lesion of eyephills, perform dark-field examinations before amoxicillin therapy and monthly serological tests for at least four months. In chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller than recommended doses should not be used. In stubborn infections, several weeks' therapy may be required. Except for gonorrhea, continue treatment for a minimum of 48-72 hours after patient is asymptomatic or bacterial eradication is evidenced. Treat hemolytic streptococcal infections for at least 10 days to prevent acute rheumatic fever or glomerulonephritis.

Supplied: Amoxicillin as the trihydrate: Capsules, 250 mg and 500 mg; oral suspension, 125 mg/5 ml and 250 mg/5 ml; pediatric drops, 50 mg/ml.

Larotid

the oral broad spectrum
antibiotic formerly
named Larocin 



Tribune Economic Analysis



Selling Price and Market Volume
By Ask Janeway
Contributing Editor

There's a simple way to resolve the apparent riddle about stock market prices. It's not by nging over the price trend, but by recognizing the plain, unarguable meaning of the volume trend. Volume is not just down; it has collapsed into a bottomless pit.

The August stock market buying panic had a double impact on volume. It began by expanding volume to a new peak; and ended by making inflated stock prices dependent on still new volume peaks for their stability. The 1975 high for volume—35 million shares a day—is an eyebrow raiser. The depth of the subsequent collapse speaks for itself.

In the wake of the buying panic, I ventured the guess that the market would need to do 35 million shares a day just to hold its gains, and no less than 40 million shares a day to extend them. The gains were guaranteed to send sellers scrambling to turn stocks back into cash. Moreover, the sellers were likely to be the owners of big blocs accumulated in the years when the fundamentals warranted a simple vote of confidence in holding stocks. The uncertainties developing have been clearly persuading more substantial investors to lighten their holdings.

More buying has been needed to absorb the buildup in selling volume. Instead, buyers have been scared off and sellers locked in.

Volume has now sometimes shrunk to under 12 million and even 11 million shares daily. More ominous still, volume has taken to making new lows on days when prices have been firm or even rising. This divergence between the volume and the price trend is enough to show that the main rift of the market is again downward, and that its rallies are now corrections.

If volume is indeed proved the forerunner of prices, a corresponding two-thirds drop in the Dow from its old double top of 1,000 would collapse it towards 300.

Ask Janeway

I am a 45-year-old divorced R.N. and am going back to nursing after a very long absence.

My brother-in-law advises me to take \$20,000 out of my portfolio and put it into foreign government bonds at 11 per cent. What do you think of that?

Midwest R.N.

Your brother-in-law's suggestion is not impressive. Triple B-rated U.S. Utility bonds are yielding above 11 per cent, and they are safer than foreign bonds.

Send your questions on finances, investments, taxes to Janeway, MEDICAL TRIBUNE, 880 Third Avenue, New York, N.Y. 10022

Emotional Problems Drop Residents from Psychiatry

Continued from page 16

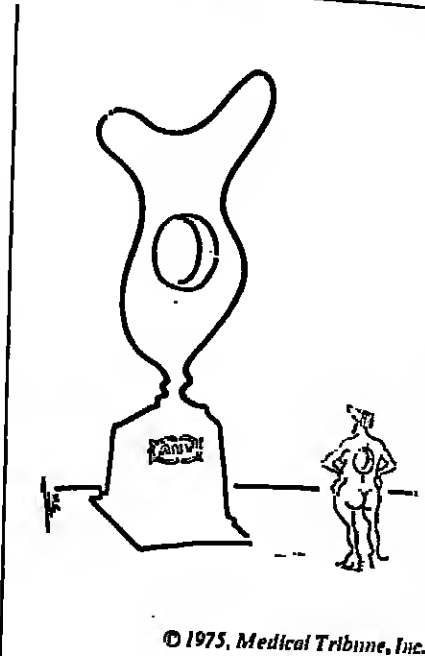
Zebulon C. Taintor, a psychiatrist and director of Multi-State Systems, Rockland Research Center in Orangeburg, New York.

"The small size of the group who left for academic or miscellaneous reasons confirms our impression from experience that residents who exhibit difficulties severe enough to lead to termination do so independent of emotional disturbance," the AADPRT task force report concluded.

The study findings also contradicted the widespread belief that minority groups in psychiatric residency programs constitute a high risk for en-

countering problems during residency. "Contrary to our expectations, we found that women, ethnic minorities, and FMGs had a significantly lower incidence of marginal performance or emotional problems than their distribution in the total residency population would suggest," Dr. Russell said.

In an effort to help curb the problem of emotionally disturbed residents, the task force recommended that program directors make every effort to identify the factors common among residents who become emotionally ill, and provide the support necessary to keep those problems from reaching crisis proportions.

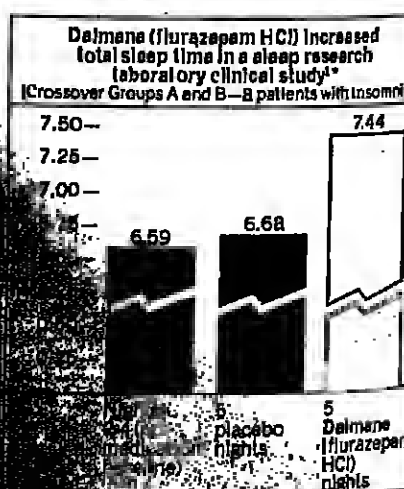


© 1975, Medical Tribune, Inc.

Taking action against this common form of insomnia...

For your patients with trouble sleeping long enough: increased sleep time...

In a 17-night clinical study¹ in the sleep research laboratory, Dalmane® (flurazepam HCl) was compared with placebo. As shown below, Dalmane produced a clear-cut improvement in total sleep time. This ability of Dalmane to increase total sleep time was corroborated in four geographically separated studies, and was shown to be predictable and reproducible from one study to another.^{2,3}



And for those with trouble falling asleep or staying asleep...

...the evidence on Dalmane is just as impressive. These and other sleep research laboratory clinical studies^{1,2} prove: Dalmane induces sleep rapidly, reduces number and duration of nighttime awakenings.

Dalmane (flurazepam HCl) is relatively safe, seldom causes morning "hang-over". Dalmane is generally well tolerated at the usual adult dosage of 30 mg; in elderly and debilitated patients, an initial dose of 15 mg is recommended to help preclude oversedation, dizziness or ataxia.

REFERENCES:

1. Kales A, et al. *Clin Pharmacol Ther* 19:691-697, July-Aug 1971
2. Frost JD Jr. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
3. Vogel GW. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
4. Dement WC. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ
5. Karacan L, Williams RL, Smith JR. The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
6. Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley NJ

Before prescribing Dalmane (flurazepam HCl), please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring relief of sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, light-headedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably

indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, lightheadedness, difficulty in focusing, blurred vision, burning eyes, lightheadedness, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubin and alkaline phosphatase. Paradoxical reactions, e.g., excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. **Adults:** 30 mg usual dosage; 15 mg may suffice in some patients. **Elderly or debilitated patients:** 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

Depend on highly predictable results with

Dalmane®
(flurazepam HCl)

One 30-mg capsule h.s.—usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule h.s.—initial dosage for elderly or debilitated patients.

Objectively proved in the sleep research laboratory:

- sleep for 7 to 8 hours, on average, with a single h.s. dose
- sleep with fewer night time awakenings
- sleep within 17 minutes, on average



ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Apparent Hyaline Disease May Be Strep B



Sample of lung tissue above is from patient who died after sudden onset of what appeared to be hyaline membrane disease, but was, in fact, an overwhelming group B strep infection. Arrow shows gross positive cocci in chains and pairs. Many cocci are visible elsewhere in slide, but no inflammatory cells.

Continued from page 1

ologists. Jaundice and hyperbilirubinemia were observed in most of the patients.

The clue to a differential diagnosis, another team member said in an interview, is the acute onset of respiratory distress. "The development of apnea suggests hyaline membrane disease, but the suddenness is not characteristic of this disease, which is more gradual in onset," declared Dr. Tim Miller, Director of the Premature Intensive Care Unit at St. Francis.

With group B strep infections "now recognized as the number one cause of death" in neonates due to septicemia, Dr. Baman urged the importance of both swift therapeutic measures and an

immediate culture at the first sign of infection.

His warnings came in a report on 21 infants with group B streptococci studied at the hospital. Eleven had sepsis, 10 had group B colonization. There were nine deaths in the series, from seven hours to four days after birth, with seven of the deaths occurring in the septicemic series.

In the latter group, the infants were premature or underweight or both. Of the 10 neonates with group B colonization, none showed any of the clinical symptoms seen in the sepsis group. Dr. Baman noted, Precautionary cultures were taken in this group, however, because of the prolonged rupture of the fetal membranes—17 hours or longer in duration.

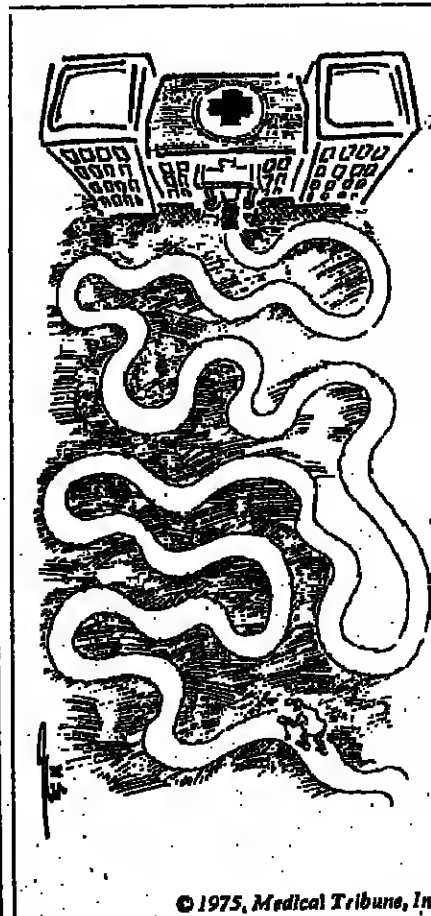
High Degree of Suspicion

In his interview, Dr. Miller stressed: "Physicians should be aware that infants most at risk of dying from B strep infections are those of low birth weight or of low gestational age. Their clinical picture is exactly like that of hyaline membrane disease. If these babies are born in outlying hospitals, they should be transferred as quickly as possible to a center where respiratory care can be offered. We think that if the baby exhibits respiratory distress, he should have an appropriate culture taken and antibiotics started prior to transport. As for the problem of B strep colonization, again there must be a high degree of suspicion in infants of low gestational age and low birth weight, because the disease kills so quickly."

He noted that at autopsy in the septicemic neonates, "The organism is an ever-whirling, you can see it microscopically in the lung tissue."

Dr. Baman added: "The infant's chest x-ray is usually interpreted as hyaline membrane disease, or pneumonia or bilateral infiltrate. But if you make a Gram stain, you see the organism everywhere."

Contributor was Dr. C. E. Kelly, Associate Pathologist.



© 1975, Medical Tribune, Inc.

Current Opinion

The Importance of Being Earnestly Critical

Continued from page 14
School (*Diabetes*, 21:1173, 1972) found that "in human beings with diabetes, good control improves the state of myelination of already damaged nerves, (for when blood sugar is controlled the accumulation in nerves of the products of the sorbitol pathway may be minimized)."

Nature of Diabetic Lesion: The Sorbitol Pathway

JUST AS HYPERLIPIDEMIA appears to increase the deposition of its metabolically inert component, cholesterol in arterial tissue contributing to atherosclerosis, so too does hyperglycemia add to the deposition of a metabolically inert by-product, sorbitol, which accumulates intracellularly in a number of tissues. Unlike muscle and adipose tissue which require insulin to effect the passage of glucose into their cells, other tissue cells do not require the agency of insulin for penetration of glucose; they, being freely permeable to glucose, the ambient blood glucose level determines the intracellular glucose, and with hyperglycemia intracellular glucose is increased. Within the cells, the inert sugar alcohol sorbitol is formed from glucose by the enzyme aldose reductase. This and other sugar alcohols once formed are trapped intracellularly, contributing to hypertonicity within the cell.

As summarized by K. H. Gabbay (*New Eng. J. Med.* 288:831, 1973), "Recent investigations suggest a role for the sorbitol pathway in the metabolism of the excess glucose in the tissues bearing the brunt of diabetic manifestations (lens, retina, nerve, kidney, blood vessels and islet cells), and an involvement in some of the diabetic tissue complications." Sorbitol, being metabolically inert, accumulates where formed, the more so with time and the higher the level of its blood glucose precursor. Intracellular sorbitol accumulation, which characterizes diabetes, is indeed proposed by U.S.S.R. endocrinologist N. Drasnin as a basic metabolic lesion of aging (*Lancet* 1:1175, May 26, 1973). He suggests possible prophylaxis of atherosclerosis, degenerative lesions of diabetes and aging by

prevention of hyperglycemia and hyperlipidemia.

New Hormonal Interrelationships in Hyperglycemia Control

THE SORBITOL PATHWAY is a new and developing concept in the pathogenesis of diabetic lesions. It provides a further rationale for control of hyperglycemia. So does the insulin-glucagon interrelationship expounded by Dr. Roger Unger center on control of the blood sugar. In Dr. Unger's view, diabetes is a bihormonal abnormality, i.e., glucagon excess of the pancreatic alpha cells as well as insulin deficiency of the beta cells. Nor are these two hormones all. Glucagon suppression with pituitary somatostatin markedly reduces hyperglycemia facilitating glucoregulation and control of hyperglycemia with only a fraction of the insulin otherwise required. Somatostatin has a broad suppressing effect on hormones other than glucagon, including growth hormone, insulin itself and a variety of hormones of the upper gastrointestinal tract which influence pancreatic hormone release of insulin and glucagon. Indeed, very recently evidence has been adduced that somatostatin is not confined to the pituitary and hypothalamus but may be a natural component of the gut and pancreas, and a master hormone in regulating glucose metabolism by its mediating action on other hormones of the gut and pancreas (*Lancet* 1:1323, June 14, 1975).

Hyperglycemia Control Remains Key to Diabetes Therapy

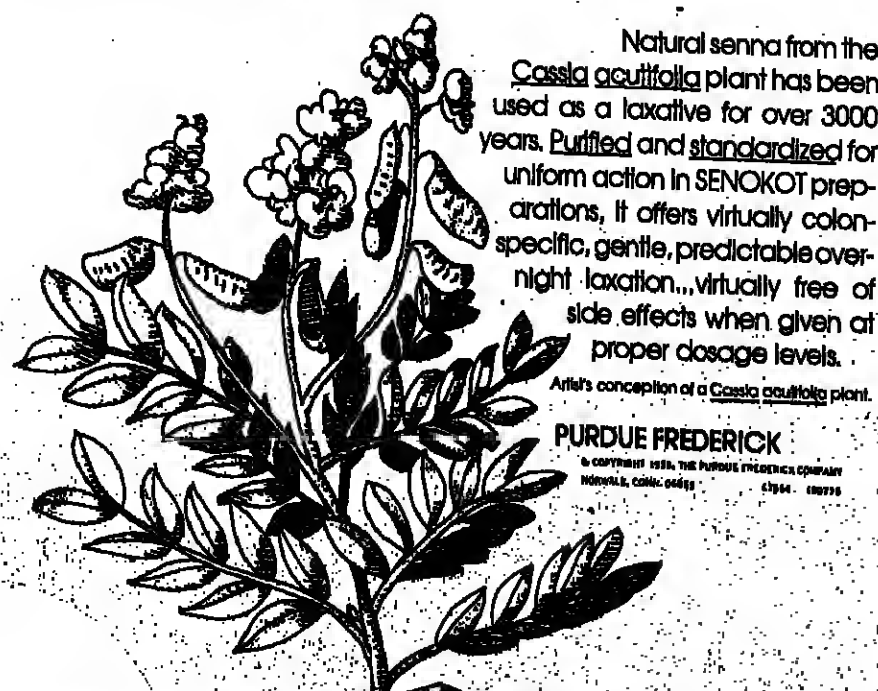
IT IS OF PARTICULAR INTEREST that with all the rapidly evolving new concepts in diabetes—the sorbitol pathway, the insulin-glucagon bihormonal regulation of blood glucose, the suppressive effect of somatostatin on glucagon and other hormones facilitating control of blood sugar—one tenet remains, i.e., the importance of regulating blood sugar and preventing hyperglycemia.

New physiologic understanding explains what has been documented clinically in long-term follow-up studies, namely that the well-controlled diabetic, as judged by regulation of the blood sugar, fares much better with respect to survival and complications than diabetics who are not well controlled. The finding that diabetics who are not well controlled exhibit a mortality two-and-a-half times greater than those who are well controlled, observed in the earlier Equitable Life study in which the writer collaborated, has been found precisely the same in the greatly extended twenty-year mortality study by Goodkin.

It seems clear that control of hyperglycemia in diabetes is important. When this can be accomplished by diet alone, it is, of course, desirable to do so. Hopefully in the future the recently discovered beneficial effect of somatostatin will lead to the development of new approaches to regulate blood sugar. Until such time, other hypoglycemic agents which have had very extensive clinical use, insulin, the sulfonylureas and the biguanides are available to offer, together with diet, versatile approaches to managing the diabetic patient. There appears to be no basis to alter present clinical use of the sulfonylureas or the biguanides.

In this age of synthetics
you can choose a natural vegetable laxative

Senokot tablets
(standardized senna concentrate)
granules



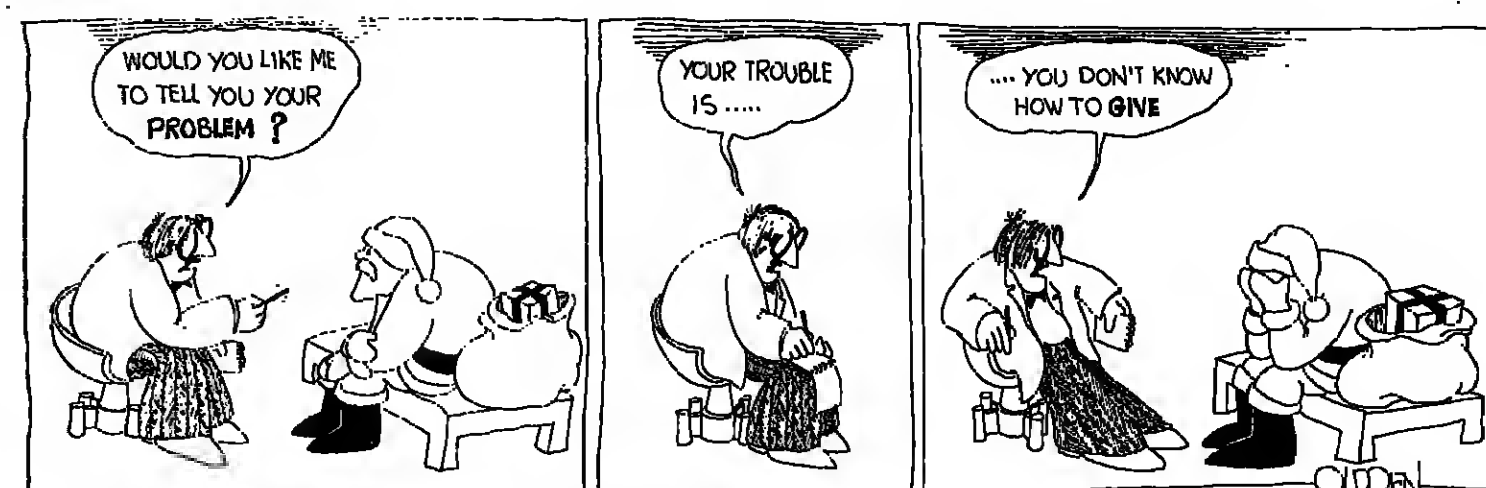
Natural senna from the *Cassia acutifolia* plant has been used as a laxative for over 3000 years. Purified and standardized for uniform action in SENOKOT preparations, it offers virtually colon-specific, gentle, predictable overnight laxation...virtually free of side effects when given at proper dosage levels.

Art's conception of a *Cassia acutifolia* plant.

PURDUE FREDERICK
A DIVISION OF THE PURDUE PHARMACEUTICAL COMPANY
INDIANAPOLIS, INDIANA 46206

Clinical Trials

By Oldden



TRIBUNE SPORTS REPORT

New Guidelines May Improve Safety of Judo Participation



Investigators suggested that more falling practice and a study of gymnastics would help students orient themselves in space quickly. The need for both is obvious.

Medical Tribune Report

NEW ORLEANS—A study of judo injuries by three California physiatrists, undertaken to assess the safety of judo bouts, has underscored the need for better methods of recording injuries and produced new guidelines for judo participation.

Dr. Mas Yamamoto, a Sacramento internist, and Drs. Thomas Devlin of Santa Cruz and Joseph J. Fitzsimmons of San Jose (both orthopedic surgeons and judo buffs), based their report to the American Orthopedic Society for Sports Medicine, meeting here, on 14,323 contestants and 20,567 bouts from

1969 to 1973. In addition, 90 Shiais (tournaments) were included.

"It is difficult during a tournament to obtain all the information needed before one of the participants disappears or the doctor is called away to another injury," the authors observed.

"We feel the best answer to this would be a Sempai-Kohai relationship of the doctor and an interested Black Belt." (Sempai and Kohai, they said, denote ranks in judo expertise; Sempai is higher.)

They also recommended Kohai rank as a qualification for a referee of a national tournament. The referee

"should touch and check each injury with the doctor while on the mat and help keep books." Referees, they found, often neglect their duty to penalize "overly zealous but incompetent contestants."

To avoid injuries from legitimate moves, "it might be well that a study of gymnastic techniques is in order, so the student can learn to orient himself in space quickly and easily," they added.

They also observed that:

- The type of mat, exclusive of a thin horseshoe wrestling mat, does not affect injury rates.
- A "springing" floor does seem to reduce injuries.
- Certain maneuvers should be restricted to bouts between higher-ranking contestants.
- More Ukeni (falling) practice is needed from all positions.
- The contestant who has been stunned should give serious consideration to withdrawal from the tournament.
- Anyone who sustains a concussion or traumatic loss of consciousness should withdraw immediately without question.

Bloody noses, sore or sprained toes and ribs, chokes and arm bars, and complaints with no positive physical findings were not listed as injuries in the study, the authors said. Nevertheless, because of problems in reporting injuries, "the ratio of injuries to bouts for national tournaments appears to be innocuous when compared to promotional [tests to qualify for higher rank], but this is very deceptive."



Study of judo injuries found that certain maneuvers should be restricted to bouts between higher-ranking students.

IMMATERIA MEDICA

Speaking of Tidal Waves

"We liked," says Dr. G. G. Heit of New York, "the opening line of Ernest Leogrande's review of the Japanese-American film *Tidal Wave*, which is advertised as 'the ultimate disaster.' It reads: 'Japan is slowly sinking into the ocean, the ultimate travelogue.'"

It sure brings back memories of all those sound track narrations that ended "And now we leave... sinking in the setting sun."

Hot Seats

From Floresville, Texas, Dr. Sam A. Nixon has enlivened our day with an excerpt from the Bulletin of the American Association of Public Health Physicians in Austin that reports on a new resolution concerning smoking restrictions in places of public assembly in New York. The new resolution provides:

"—Restaurants with 51 or more seats must set aside at least 220 percent of them for nonsmokers."

Overkill!!!, says Dr. Sam.

The Swiss Connection

GENEVA, SWITZERLAND—Pharmacists in Switzerland, faced by an increasing number of break-ins by persons seeking drugs, have come up with a Swiss solution. Drugs liable to addiction or abuse are being stored at night in the vaults of local banks.

It's the old Swiss connection—too logical for words.

Clinical Cliché



Early spillage was produced.